Opportunities for Organ Donor Intervention Research

SAVING LIVES BY IMPROVING THE QUALITY AND QUANTITY OF ORGANS FOR TRANSPLANTATION

Committee on Issues in Organ Donor Intervention Research

James F. Childress, Sarah Domnitz, and Catharyn T. Liverman, *Editors*

Board on Health Sciences Policy

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This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

We thank the following individuals for their review of this report:

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report nor did they see the final draft before its release. The review of this report was overseen by **Enriqueta C. Bond,** Wellcome Fund, and **Philip J. Cook,** Duke University. They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

Preface

Organ transplantation, a procedure that saves lives and improves quality of life, is made possible in the United States solely by the public's generous gifts of organs. For deceased organ donation, this means that individuals during their lifetimes graciously decided to be organ donors or that their grieving families made that decision. Making the most of these gifts for current and future transplant recipients is the goal of organ donor intervention research.

Donor intervention research examines the use of various medications, procedures, or other interventions that might improve the quality of donated organs or increase the number of organs that are suitable for transplantation. Such research is unique in that the outcomes of an intervention performed in one individual, the deceased donor, may directly affect and be assessed in another individual, the transplant recipient. The very brief timeframe in which this research must be conducted (to maintain organ viability and ensure transport to the recipient) and the fact that organs from a single donor may go to multiple recipients in different transplant centers throughout the United States add to the complexities of this research. These factors also heighten the need for an ethics-based framework with strong oversight mechanisms that can facilitate this research and, at the same time, respect donors' wishes and protect research participants.

The organ donation and transplantation system is built on public trust, and maintaining that trust is crucial to sustaining this system. Throughout this Consensus Study Report, the details of this system and the potential for research to improve the system are discussed from the perspectives of organ donors and recipients alike. The committee recommends a set of actions to

ensure that this research goes forward in a manner that supports trust, fairness, and respect for persons in organ donation and transplantation.

This report benefited immensely from the input and insights of many individuals and organizations. The committee appreciates the sponsors' support for this study and their work in bringing this important topic to the forefront of efforts to further the field of organ transplantation. Many individuals generously provided time and expertise to the committee as invited workshop and conference call speakers, and the committee greatly appreciates their significant contributions. The reviewers also provided insightful comments that strengthened this report.

It was my great privilege to chair this National Academies of Sciences, Engineering, and Medicine study. From the first meeting through the final report's publication, each committee member brought commitment, energy, and intellectual curiosity and rigor to this effort. The members devoted countless hours to this task and were a great pleasure to work with and learn from. The committee was supported by an energetic and knowledgeable staff that made sure that all aspects of this complex topic were thoroughly discussed and documented.

This report seeks to enable organ donor intervention research to move forward, within appropriate ethical, legal, and regulatory limits, in order to save more lives, to improve the quality of lives, and to fully honor the gifts of organs for both current and future transplant recipients.

James F. Childress, *Chair*
Committee on Issues in Organ Donor
Intervention Research

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Summary

The organ donation and transplantation system strives to honor the gift of donated organs by fully using those organs to save and improve the quality of the lives of their recipients. Organ transplantation has become the optimal treatment for many end-stage organ-specific diseases. However, there are not enough donated organs to meet the demand. Some donated organs may not be recovered, some recovered organs may not be transplanted, and some transplanted organs may not function adequately. Yet, almost all transplantation research to date has focused on transplant recipients and on ways to improve transplantation processes and post-transplant health outcomes rather than on how to enhance the quality and increase the quantity of organs that can be recovered from deceased donors and then successfully transplanted. Organ donor intervention research can test and assess interventions (e.g., medications, devices, and donor management protocols) to maintain or improve organ quality prior to, during, and following transplantation. The intervention is administered either while the organ is still in the deceased donor or after it is recovered from the donor but before it is transplanted into a recipient.

Organ donor intervention research presents new challenges to the organ donation and transplantation community because of ethical questions about who should be considered a human subject in a research study, whose permission and oversight are needed, and how to ensure that such research does not threaten the equitable distribution of a scarce and valuable resource. Therefore, organ donor intervention research requires extensive oversight and careful planning to ensure that the integrity of the donation and transplantation process is maintained and that fully

using the gift of the donated organ has the highest priority in all phases of research.

THE DEMAND FOR ORGAN TRANSPLANTATION

The number of organs transplanted has increased in recent decades. In 2016, approximately 82 percent of organs transplanted in the United States were from deceased donors—27,630 organs were transplanted from 9,971 deceased individuals, while an additional 5,980 organs were transplanted from living donors. In comparison, 10,794 organs were transplanted from deceased donors in 1988, and an additional 1,829 organs were transplanted from living donors. The outcomes for transplant recipients, including graft survival, have also improved. However, the growth in the number of patients awaiting organ transplantation has outpaced the growth in the number of organs being transplanted (see Figure S-1). As of July 13, 2017, there were 117,154 transplant candidates awaiting an organ.

The supply of organs available for transplantation is affected by several factors including the number of potential organ donors and the public's willingness to donate organs. Additionally, every year a number of of donor organs are not transplanted (see Figure S-2). For example, donated organs may not be transplanted because of the condition of the donated organ or because it is not possible to allocate an organ within the timeframe during which the organ is viable for transplantation. A donated organ may be determined to be unsuitable for transplantation based on a variety of factors such as the health of the deceased donor, the cause of death, or functional or anatomic abnormalities found in a potential donor or donor organ.

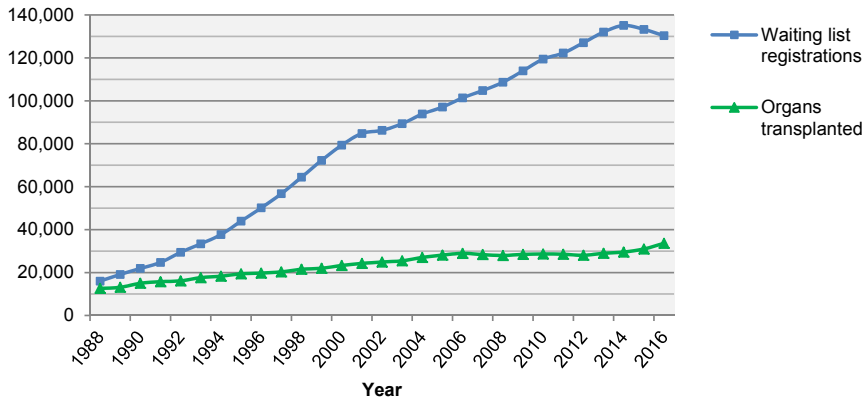

FIGURE S-1 National transplant waiting list registrations for all organs (as of December 31 each year) and organs transplanted (living and deceased donors) by year.

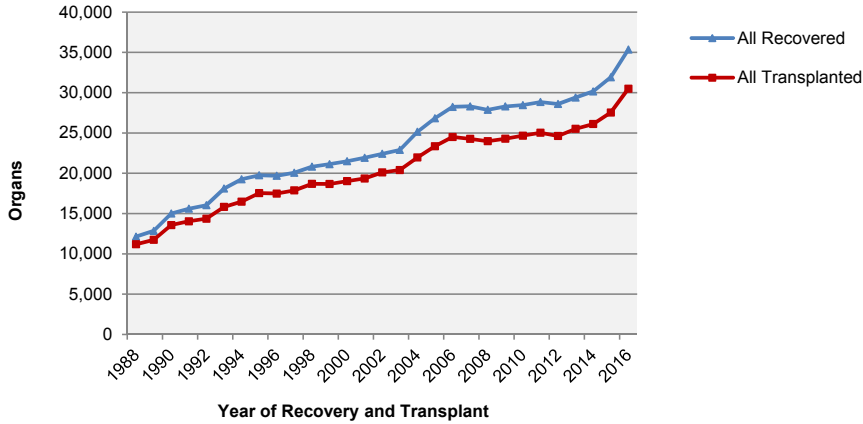

FIGURE S-2 Number of deceased donor organs that were recovered compared with the number that were transplanted, 1988–2016.

STUDY PROCESS AND TASK

This report focuses on the ethical, legal, regulatory, policy, and organizational issues relevant to the conduct of research in the United States involving deceased organ donors.[1] This type of research is challenging to conduct under current policies and regulatory mechanisms concerning biomedical research. For these reasons, a group of organizations came forward to sponsor a study by the National Academies of Sciences, Engineering, and Medicine (the National Academies) on deceased organ donor intervention research: American Association for the Study of Liver Diseases, American Society of Transplant Surgeons, American Society of Transplantation, Association of Organ Procurement Organizations, Gift of Life Donor Program, Health Resources & Services Administration, Laura and John Arnold Foundation, National Institutes of Health (National Heart, Lung, and Blood Institute; National Institute of Allergy and Infectious Diseases; National Institute of Diabetes and Digestive and Kidney Diseases), National Kidney Foundation, OneLegacy Foundation, and The Transplantation Society. To address the statement of task (see Box S-1), the National Academies appointed a 12-member committee with expertise in organ transplant surgery, organ procurement, pediatrics, decision science, law, ethics, clinical trial research, and organ donation public awareness and education efforts.

[1] Living donation is not included in the statement of task and thus not discussed in this report.

Box S-1 STATEMENT OF TASK

An ad hoc study will examine the ethical, policy, regulatory, and organizational issues relevant to the conduct of research involving deceased organ donors (for purposes of the study, the concept excludes interventional research preceding declaration of death by neurologic or cardiopulmonary criteria among potential organ donors). The committee will examine the gaps, barriers, and opportunities for clinical research involving deceased donors that aims to increase the quality and quantity of donated organs available for transplantation, with particular attention to interventions administered to the donor and thus potentially affecting all of the donor's organs.

Specifically, the report will delineate the issues pertinent to organ donor intervention research and make recommendations that take into account public and professional trust in the organ donation process and ethical conduct of organ donor intervention research with attention to

- Ethical principles relevant to the conduct of interventional research on deceased donors and deceased donor grafts
- Responsibilities to donors and donor families
- Roles and responsibilities of donor hospitals
- Responsibilities to patients awaiting organs
- Responsibilities to transplant recipients of organs from donor intervention studies
- Delineation of ethical and regulatory oversight considerations specific to the safety of patients impacted by the study interventions (recipients of organs that were the target of the research intervention, and recipients of organs that were exposed to a research intervention but were not the targeted organs under study)
- Oversight and monitoring of organ donor intervention research, including addressing issues relevant to the type of review and oversight needed for
  - Evaluation of the scientific validity and potential efficacy of interventions in deceased donors to mitigate organ injury
  - Ethical framework for reviewing and evaluating conduct of clinical trials involving donor interventions
  - Evaluation of the impact on organ distribution with respect to waitlist morbidity and mortality
  - Review of the impact on transplant outcomes for all organs exposed to the intervention
- Impact on the distribution of research organs within the national system, and the implications for patients, health systems, investigators, donation professionals, organ procurement organizations, transplant professionals, and transplant centers

After examining the complexities and challenges surrounding organ donor intervention research, the committee identified six goals to guide its work (see Box S-2).

This report provides recommendations for how to conduct organ donor intervention research in a manner that maintains high ethical standards,

Box S-2 COMMITTEE'S GOALS FOR THE STUDY

- Improve transparency and public trust in the organ donation process for research followed by transplantation.
- Improve the coordination and sharing of information about donor preferences.
- Clarify legal guidance on organ donation for the purpose of research followed by transplantation (organ donor intervention research).
- Promote informed consent for transplant recipients' participation in organ donor intervention research in a manner that is compatible with the logistical complexities of organ transplantation.
- Establish centralized management and oversight of organ donor intervention research in order to ensure equitable, transparent, and high-quality research.
- Promote transparency regarding organ donor intervention research and enable the implementation, tracking, and analysis of organ donor intervention research to improve transplantation outcomes.

that ensures dignity and respect for deceased organ donors and their families, that provides transparency and information for transplant candidates who might receive a research organ, and that supports and sustains the public's trust in the process of organ donation and transplantation.

THE ORGAN DONATION AND TRANSPLANTATION PROCESS

In the United States, organ donation and transplantation are accomplished through a cooperative, interdependent network of multidisciplinary, multi-institutional services. Oversight of this highly regulated process is coordinated by the federally mandated Organ Procurement and Transplantation Network (OPTN), which is operated by the United Network for Organ Sharing (UNOS). OPTN sets national policies that apply to all organizations involved in organ donation and transplantation, including organ procurement organizations (OPOs), donor hospitals, and transplantation programs and centers. Currently, 58 OPOs procure and distribute organs to 254 transplant hospitals. Different programs within these hospitals are responsible for the transplantation of specific organs and the follow-up care for organ transplant recipients. An extensive national computerized network is used to match donated organs with potential recipients. The network operates in units referred to as donation services areas (DSAs). Each DSA encompasses one OPO, the donor hospitals contracted to work with the OPO, and the assigned transplant hospitals, transplant programs, and histocompatibility labs that serve the area. DSAs are geographically and culturally diverse and work within the nation's 11 transplant regions.

Individuals who need an organ transplant are placed on a waiting list for the type(s) of organ they need. When an organ becomes available and a potential recipient is identified, the potential recipient's transplant team is notified and provided with details about the organ. If the organ is determined to be acceptable, the team contacts the potential recipient to determine his or her current state of health and interest in proceeding with the transplantation. In order to maintain the organ in optimal condition, the decision of whether to accept an organ offer needs to be made quickly—usually within 1 hour of the recipient team receiving the offer and accessing the deceased donor's information—and the transplantation surgery proceeds as soon as possible after the organ is accepted and received.

THE POTENTIAL OF ORGAN DONOR RESEARCH

In the time between the declaration of the donor's death and the procurement of the organs, the authorized OPO and donor hospital implement donor management protocols (e.g., administering medications and maintaining the donor's body at a particular temperature). These protocols are designed to maintain the organs in the best possible condition by minimizing the organ stress, damage, and dysfunction until the organs are recovered.

If research followed by transplantation (organ donor intervention research) has been authorized, the research intervention would be administered to a deceased donor prior to organ recovery or to the target organ after the organ has been recovered but before transplantation. When the research intervention is administered prior to organ recovery and the intent is to have an effect on a specific organ (i.e., the target organ), the intervention could affect other organs from the same donor that may also be removed and transplanted after the intervention (i.e., non-target organs). As a result, many transplant recipients across multiple transplant centers could become human subjects in a single organ donor intervention research study. Organ donor intervention research therefore involves three different parties as potential participants in the research—organ donors, target organ recipients, and non-target organ recipients—with each deserving specific considerations, all of which are needed to ensure that a respectful, fair, and trustworthy donation and transplantation system is in place in the United States.

Deceased organ donor intervention research offers an opportunity to gain the knowledge needed to maximize the benefits of the gifts of donated organs. The committee's work focused on identifying next steps in overcoming challenges so that such research can be conducted in the pursuit of improving the quality and increasing the quantity of organs available for transplantation.

ETHICAL PRINCIPLES

The committee considered its task under the assumptions that organ transplantation is a good that is worth pursuing and expanding and that it is thus important to increase the number of and improve the quality of organs for transplantation in order to save lives and improve recipients' quality of life. A close analysis of the relevant ethical principles indicates several conditions under which organ donor intervention research can be both ethically justified and ethically conducted. These principles include

- *Respect for persons:* respect for persons' autonomous choices
- *Beneficence (utility):* balance of probable benefits against probable harms
- *Fairness:* equitable distribution of benefits, risks, costs, and burdens
- *Validity:* generation of evidence that is sufficiently reliable to guide decision making
- *Trustworthiness:* confidence in and reliance on others to act competently and in accord with ethical principles and legal and regulatory standards

Much depends on developing a clear understanding of this research, what is required for it to succeed, and how various options in its pursuit might fulfill these ethical principles.

LEGAL, REGULATORY, AND POLICY FRAMEWORKS

Ethical principles are often embodied and embedded in laws, regulations, and policies. A good example is the Uniform Anatomical Gift Act (UAGA), some version of which guides the transfer of organs from deceased persons in each state, the District of Columbia, and Puerto Rico. Another good example is the Federal Policy for the Protection of Human Subjects (also termed the Common Rule), which is the core federal policy that governs federally funded and much privately funded research involving human subjects in the United States. Trust in the U.S. donation and transplantation system, including confidence and reliance that the organizations and health professionals involved will fully and fairly communicate the facts and the nuances of the complex donation and transplantation processes, is essential. However, questions remain as to what the transplantation community and society as a whole *should* do to maintain that trust, as opposed to what merely *must* be done to be in legal and regulatory compliance.

Improving Transparency and Public Trust in the Process of Authorizing Organ Donation

The United States' organ donation system operates under an "opt-in" model in which the individual while alive or the next of kin or surrogate after the individual's death must explicitly choose to donate organs. The Common Rule defines its regulations as covering living individuals and so does not apply to deceased organ donor intervention research itself. However, authorization for organ donation, including for research purposes, is still required under state laws based on the UAGA. The challenge is that the state laws vary regarding authorization for research followed by transplantation and there is no standard practice for recording an individual's preferences for donating organs for the purpose of research followed by transplantation. Additionally, there are no requirements for what information about organ donation options, including research, should be provided to individuals who are contemplating registering to be an organ donor.

Messaging and communication strategies regarding organ donor intervention research need to be developed and thoroughly tested to meet the health literacy needs across the general public. It will be important to identify the potential benefits of organ transplantation with organs that have been subject to organ donor intervention research in awareness and educational programs about organ donation. This is particularly important for populations who may be suspicious of research because of a long history of biomedical research abuses. Racial and ethnic minorities tend to have lower rates of organ donation and to be less willing to participate in research. Social and economic marginalization, as well as distrust in medical research that has its roots in historical abuses, have likely made members of minority groups less likely to participate willingly in organ donation and research.

Recipients of Research Organs: Improving Consent and Ensuring Protections

The committee examined the effective and ethical implementation of the laws that ensure human research subject protections with particular attention to the following questions:

- Are recipients of research organs human research subjects?
- What are the issues regarding informed consent?
- How can the informed consent processes use risk stratification?
- How can consent be most effectively obtained given the time-sensitive nature of these decisions?
- What are the issues for post-transplant follow-up?

These questions raise a number of ethical and regulatory issues and the committee's conclusions are summarized in Figure S-3.

Careful consideration is needed for how to most effectively inform transplant candidates about organ donor intervention research. The window of time during which an organ is viable for transplantation and during which many steps in the transplantation process must take place is limited. Additionally, transplant candidates receive a wealth of information from the time of intake through the time of discussing a transplant organ offer and need adequate time to fully learn about organ donor intervention research and make a determination about whether they would consider receiving a research organ.

In order to find a balance between the laws and regulations and the need to ensure that organs do not become unusable because of an excessive lapse of time, the committee proposes a two-stage process for obtaining consent from transplant candidates who could receive a research organ. In the first stage, information on organ donor intervention research is provided and the transplant candidate is asked to decide whether they would consider receiving a research organ. This first stage would be part of the clinical consent process that begins at the time of patient intake and continues through wait listing. The second stage would occur when an organ is being offered to the transplant candidate and would follow research informed consent processes as determined by the single institutional review board (IRB) for organ donor intervention research. The committee considered other options that would require revisions to the Common Rule, but concluded that the proposed two-stage process should stay within current human research subjects protection regulations and that this process offers the best opportunities to

- fully inform transplant candidates about organ donor intervention research at a time when they can consider the risks, benefits, and alternatives in depth;
- provide a thorough informed consent process for participation in research; and
- allow the process to be conducted as expeditiously as possible by only doing the more in-depth informed consent processes with those candidates who have expressed an interest in receiving a research organ.

GOAL 1: ***Improve transparency and public trust in the organ donation process for research followed by transplantation.***

RECOMMENDATION 1: The Organ Procurement and Transplantation Network, organ procurement organizations (OPOs), the Health

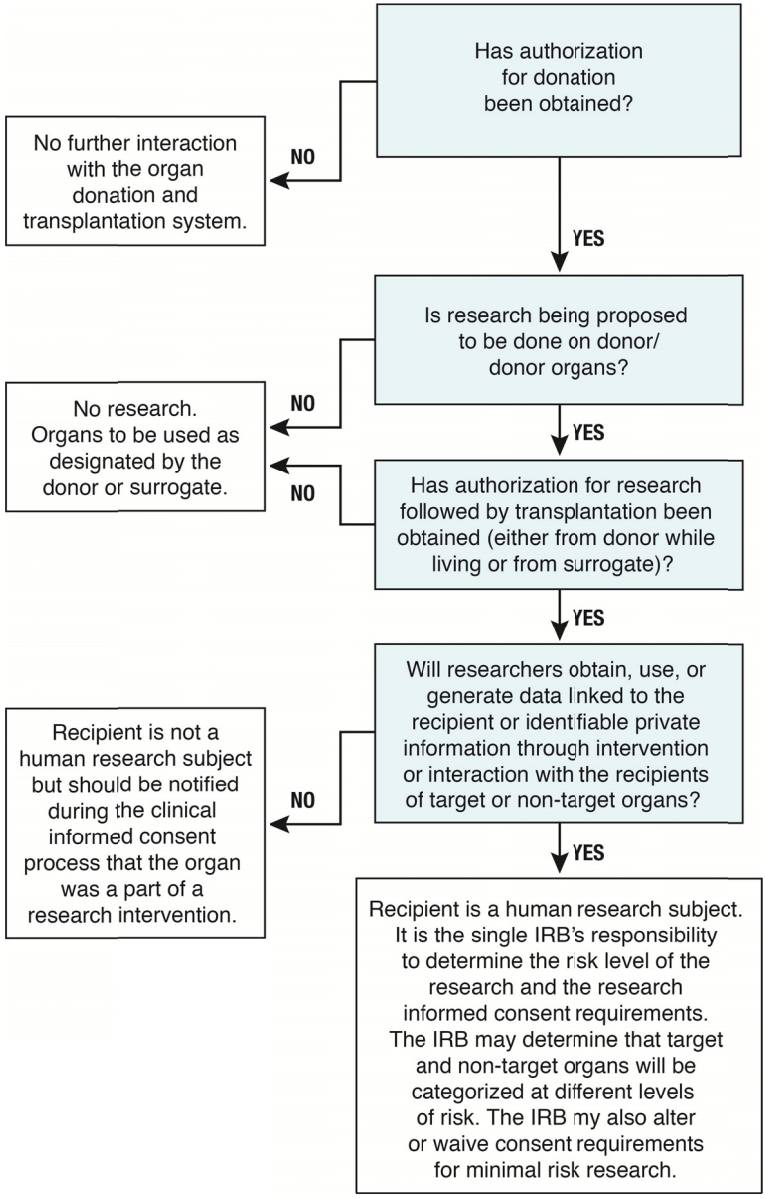

FIGURE S-3 Research authorization and consent decision points.
NOTE: IRB = institutional review board.

Resources & Services Administration, advocacy organizations, and professional associations involved in educating the general public and obtaining individual and surrogate authorization should explore, develop, and test communication strategies and materials that explain organ donor intervention research and should implement and disseminate those resources for which effective messaging has been identified. Information resources to be developed include

- **Template language to be used by all U.S. organ donor registries (e.g., departments of motor vehicles [DMVs], national registry) to ensure consistency across registries in the language used to obtain authorization for organ donation. This language should explain organ donation options in language that takes into account the wide range of degrees of health literacy among the public.**
- **Templates for DMVs, OPOs, and other entities that advocate for organ/tissue donation to use for communicating a consistent set of facts about organ donor intervention research across websites and other dissemination methods.**
- **Standardized talking points for communicating with donor surrogates and families about organ donor intervention research. These should include, at a minimum, information about donation, transplantation, and research in language that takes into account the wide range of degrees of health literacy among the public.**

GOAL 2: ***Improve the coordination and sharing of information about donor preferences.***

RECOMMENDATION 2: All active donor registries in the United States should coordinate in order to ensure a single, unified secure national donor registry that is easily accessible to organ procurement organizations. All donor registry information collected by departments of motor vehicles should automatically feed into this single national registry. Model state legislation should be developed to facilitate this merger.

GOAL 3: ***Clarify legal guidance on organ donation for the purpose of research followed by transplantation (organ donor intervention research).***

RECOMMENDATION 3: The National Conference of Commissioners on Uniform State Laws should explore revisions to the Uniform Anatomical Gift Act (UAGA) that would clarify the authorization of organ donation for the purpose of research followed by transplanta-

tion. The following possible clarifications to the UAGA should be considered:

- **When a decedent has stated a general intent to make an anatomical gift, without further specification, research followed by transplantation is permitted.**
- **Organ procurement organizations should be explicitly empowered to seek from a donor's surrogate the expansion of the authorization for an existing gift for any purpose to be used for research followed by transplantation.**

The committee also considered two options for resolving the ambiguities in the UAGA and state laws, but sensitive to trust and transparency felt this issue requires more public consultation. Therefore, the committee recommends that the Organ Procurement and Transplantation Network and transplant community should engage in public consultation and determine whether to amend the UAGA and state laws to

- **Specify that when the decedent has authorized transplantation this denotes that the gift is authorized for research followed by transplantation, or**
- **Specify research followed by transplantation as an additional purpose of donation that would be added to the list of choices for the donor.**

GOAL 4: ***Promote informed consent for transplant recipients' participation in organ donor intervention research in a manner that is compatible with the logistical complexities of organ transplantation.***

RECOMMENDATION 4: Transplant centers and organ procurement organizations, in collaboration with the Organ Procurement and Transplantation Network/United Network for Organ Sharing, professional associations, and patient advocacy organizations should develop and implement a protocol for notifying and educating potential organ transplant recipients about the possibility of being offered an organ that has been exposed to a research intervention and seeking informed consent if they agree to be part of the research study. Specifically,

- **At intake and at regular intervals thereafter, all potential recipients should be provided with information about organ donor intervention research and asked whether, at the time of organ offer, they would potentially consider accepting an organ (target organ or non-target organ) that was part of a research study. As a result of**

time constraints at the time of the organ offer for transplantation, only potential recipients who have previously agreed to consider research organs should be approached with the option to accept an available research organ.

- **At the time of being offered an organ for transplantation, each transplant candidate who will potentially receive an organ that is part of a research study—be it a target organ or a non-target organ—should be provided with information about the specific research protocol and should follow the single institutional review board's approved informed consent process for participating in that specific research study (including possible alteration or waiver of informed consent) and accepting the particular research organ offered. Given the importance of minimizing delays, information about the research protocol should be imparted through a process that ensures equitable, effective, and efficient placement and transplantation.**

RESEARCH APPROVAL, IMPLEMENTATION, AND OVERSIGHT

According to the committee's analysis, one major reason for the lag in organ donor intervention research is the lack of central oversight that is needed to overcome the complexities of this geographically and clinically dispersed research. Without a central organization that can coordinate and facilitate cooperative research among a large number of institutions, this promising research is not likely to proceed at the volume, quality, and pace needed. Moreover, oversight and monitoring are needed to ensure adherence to the relevant ethical, legal, and regulatory policies and thus to promote public trust. Several of the unique challenges to conducting organ donor intervention research illustrate the rationale for a more centralized research system:

- *Brevity of the timeframe:* Time is extremely limited due to concerns about the viability of the organs. Finding the appropriate recipient(s) and making the most of the gift of an organ or organs involves making rapid decisions, which in turn requires clearly defined, well-vetted, and centralized processes and policies.
- *Target and non-target organs:* Because much of this research is conducted prior to the recovery of the organs from the deceased donor, the intervention may have the potential to affect not only the target organ but also the non-target organs.
- *Numerous and geographically dispersed stakeholders:* An organ donor managed by 1 of the 58 OPOs in the United States can provide up to eight solid organs, each of which could be transplanted by different transplant programs across the country and allocated via varied distribution schemes. Donor intervention research in-

volving donors, donor families, OPO staff, transplant staff, and recipients (target and non-target organ) adds another layer of complexity to this already multifaceted and time-driven system.

- *Fairness:* Donated organs are a scarce and valued national resource. The critical donor organ shortage and the life-and-death nature of organ donation and transplantation require a fair and equitable system for organ allocation. Organ allocation is, for the most part, moving away from a local and regional model toward a national model in which organs can be sent across the country. An oversight system must ensure that research activities do not substantially alter the way in which organs are distributed.
- *Consistency:* Successful research requires consistency of performance across the multiple institutions and disparate geographic locations. Consistency will be best achieved through centralization of clinical oversight and IRB functions.
- *Efficiency:* For organ donor intervention research to flourish, mechanisms need to be established to coordinate and facilitate initiation and implementation of multi-center research investigations across a wide geographic area. By reducing the number of parallel and dispersed processes, a centralized oversight approach diminishes major administrative barriers.

Therefore, the committee recommends the use of a centralized oversight framework that consists of three affiliated entities: (1) a centrally administered and standing Donor-Research Oversight Committee (D-ROC); (2) a single IRB for organ donor intervention research; and (3) study-specific data and safety monitoring boards (DSMBs).

The committee envisions the D-ROC as a centrally administered standing committee. As part of its charter, D-ROC should be empowered to work with stakeholders to prioritize, review, implement, and track research protocols as well as to develop and disseminate information about organ donor intervention research. Core responsibilities of D-ROC should include

- Reviewing and prioritizing donor intervention proposals
- Assessing and monitoring the impact of organ donor intervention research on organ allocation and distribution
- Coordinating and facilitating clinical and research informatics and promoting communications
- Promoting effective trial design
- Maintaining liaisons with key external groups

The standard model of local IRB oversight for multi-site studies, in which each research institution must review and approve the research

protocol, is poorly suited to the context in which organ donor intervention studies take place. Because this type of research will likely involve coordination across multiple OPOs, donor hospitals, and transplant centers, it would be necessary to obtain consent from recipients across many sites in a short period of time and to have all potential sites in agreement with the centralized processes.

A single IRB for organ donor intervention research could oversee human research protections and ensure that processes are carried out in accord with relevant regulatory and policy requirements and guidance, particularly the Common Rule. Also, a single IRB would offer the advantages of developing and maintaining core expertise in organ donor intervention research. The committee recognizes that the IRB function could be done by (1) creating an independent central IRB or (2) contracting with an existing IRB that has appropriate scientific, ethical and regulatory expertise. The single IRB may be a free-standing (central) IRB or part of an academic medical center willing to serve as the IRB of record for the multiple sites. The committee believes that D-ROC should have flexibility in determining how to best constitute or contract out the single IRB's functions.

DSMBs are independent committees that oversee the conduct of clinical trials and serve several broad purposes. First, they review incoming data in order to assure that the risk–benefit ratio of an ongoing trial has not shifted. The DSMB would establish study-stopping criteria based on outcomes for target and non-target organ recipients. The DSMB could determine that the investigation has become unsafe for participants and thus should be terminated early. Second, DSMBs can advise on and evaluate protocol amendments. For example, DSMBs can advise on broadening eligibility criteria in order to access a wider population. Third, DSMBs can evaluate whether patients need to be informed of new developments in a trial. The DSMBs for organ donor intervention research could be organized around a single research study or a set of studies. The key will be for D-ROC to have the administrative capacity to establish DSMBs as they are needed.

GOAL 5: ***Establish centralized management and oversight of organ donor intervention research in order to ensure equitable, transparent, and high-quality research.***

RECOMMENDATION 5: The Organ Procurement and Transplantation Network, in collaboration with the National Institutes of Health, the Health Resources & Services Administration, organ procurement organizations, donor hospitals, transplantation centers and programs, professional associations, patient advocacy organizations, community representatives, and other relevant organizations, should establish and sustain a standing Donor-Research Oversight Committee (D-ROC)

to guide, coordinate, evaluate, prioritize, and disseminate research on deceased organ donor interventions. D-ROC should include the administrative structure to establish independent data safety monitoring boards to ensure the scientific integrity of organ donor intervention research and assess its risks and benefits as studies progress. A single institutional review board should be established or contracted with to ensure human subject research protections for donor intervention research studies.

GOAL 6: *Promote transparency regarding organ donor intervention research and enable the implementation, tracking, and analysis of organ donor intervention research to improve transplantation outcomes.*

RECOMMENDATION 6: The Donor-Research Oversight Committee, in collaboration with the Organ Procurement and Transplantation Network, the National Institutes of Health, the Health Resources & Services Administration, professional associations, organ procurement organizations, patient advocacy organizations, and transplant centers and programs should create organ donor intervention research electronic tools to ensure that organ donor intervention studies are listed on a publicly available website, that clinicians have the information to provide to potential recipients, that researchers can conduct studies effectively, that research outcomes are tracked and monitored appropriately, and that research outcomes are widely available in aggregate. These tools could use or link to new or current relevant databases but should, at the minimum, provide the following functions:

- **Access to real-time study information used to maintain study continuity and monitor key elements of active studies necessary for project management;**
- **Additional data fields in UNet and other relevant databases to allow for the designation of the organ as a research organ and to note other relevant information about the research protocol for clinical use and in the tracking of research outcomes;**
- **An online registry of pending, approved, active, closed, and discontinued organ donor intervention research studies; and**
- **Links to research outcome data, abstracts, and scientific publications.**

1

Introduction

The organ donation and transplantation system strives to honor the gift of donated organs by fully using those organs to save or improve the quality of the lives of transplant recipients. As a result of advances achieved through basic and clinical research over the past several decades, organ transplantation has become the optimal treatment for many end-stage organ-specific diseases. However, there are not enough donated organs to meet the demand. Furthermore, some organs may not be recovered, some recovered organs may not be transplanted, and some transplanted organs may not function adequately, all of which exacerbates the imbalance between the supply and the demand of organs. A determination that an organ is not suitable for transplantation is based on a variety of factors, such as the health of the deceased donor, the cause of death, or functional or anatomic abnormalities found in a potential donor or donor organ. To date, organ transplantation research has focused almost exclusively on transplant recipients and on finding ways to improve transplantation processes and post-transplant health outcomes. Improvements that increase the number and improve the quality of organs that are available for transplantation have been slow to come, with most of them having been developed through innovations in local practice standards. Conducting research in deceased organ donors and on organs that have been recovered from deceased donors has emerged as one means to identify new methods to improve the quality and increase the quantity of organs that can be successfully transplanted and thus, hopefully, expand the number of people receiving an adequately functioning organ.

Achieving advances in the quality and quantity of organs that can be recovered from deceased donors and successfully transplanted will require organ donor intervention research that tests and assesses clinical interventions (e.g., medications, devices, donor management protocols) that are aimed at maintaining or improving organ quality prior to, during, and following transplantation. In this type of research, the intervention is administered either while the organ is still in the deceased donor or after it is recovered from the donor but before it is transplanted into a recipient. Organ donor intervention research protocols often assess the outcomes of the intervention through follow-up of the transplant recipient. As discussed throughout this report, organ donor intervention research requires extensive oversight and careful planning to ensure that the integrity of the donation and transplantation process is maintained and that fully using the gift of the donated organ has the highest priority in all phases of this research.

Deceased organ donor intervention research has the potential to help address the growing need for organs and increase the likelihood of positive health outcomes following transplantation by identifying interventions to maintain or improve organ quality prior to, during, and following transplantation. Conducting organ donor intervention research presents new challenges to the organ donation and transplantation community by raising ethical questions about who should be considered a human subject in a research study, whose permission and oversight are needed, and how to ensure that the research does not threaten the equitable distribution of a scarce and valuable resource. Furthermore, when a research intervention is administered to a deceased donor prior to organ recovery and the intent is to have an effect on a specific organ such as a kidney (i.e., the target organ), the intervention could affect other organs that will also be transplanted afterward (i.e., non-target organs). This report provides recommendations for how to conduct this research in a manner that maintains high ethical standards, ensures dignity and respect for deceased organ donors and their families, provides transparency and information for transplant candidates who might receive an organ that has been involved in donor intervention research, and supports and sustains the public's trust in organ donation and transplantation.

THE POTENTIAL OF ORGAN DONOR INTERVENTION RESEARCH

In 2016, approximately 82 percent of the organs transplanted in the United States were from deceased donors—27,630 organs were transplanted from 9,971 deceased individuals, while an additional 5,980 organs were transplanted from living donors (OPTN, 2017f). The number of organs transplanted has increased in recent decades; for example, in 1988

only 10,794 organs were transplanted from deceased donors, with an additional 1,829 organs transplanted from living donors (OPTN, 2017f). The outcomes for transplant recipients, including graft survival, have also improved (Hart et al., 2017; Kandaswamy et al., 2017; Kim et al., 2017; Smith et al., 2017). However, the growth in the number of patients awaiting an organ transplant has far outpaced the growth in the number of organs being transplanted (see Figure 1-1). As of July 13, 2017, 117,154 candidates were on the waiting list (see Table 1-1 for the number of specific organs needed by waiting list candidates and Figure 1-2 for waiting list registrations over time). This demand far outweighs the supply. Waiting list figures underestimate true need because there are many more who could benefit from organ transplantation, but whose condition is not yet severe enough to meet the requirements for candidature on the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) waiting list or for other reasons are not on the list (Patzer et al., 2015; Goldberg et al., 2016). The supply of organs available for transplantation is affected by a number of factors, including the public's willingness to donate organs, the number of potential organ donors, the health of a given donor, the condition and likelihood of adequate function of an organ once it is recovered from a donor, and the ability of an organ procurement organization (OPO) working with OPTN/UNOS to allocate a donor organ to a recipient within the timeframe that the organ is viable for transplantation. Every year many donor organs go to waste because they are considered to be at risk of functioning poorly or not at all if they were to be transplanted. Similarly, concerns about a donor's medical and

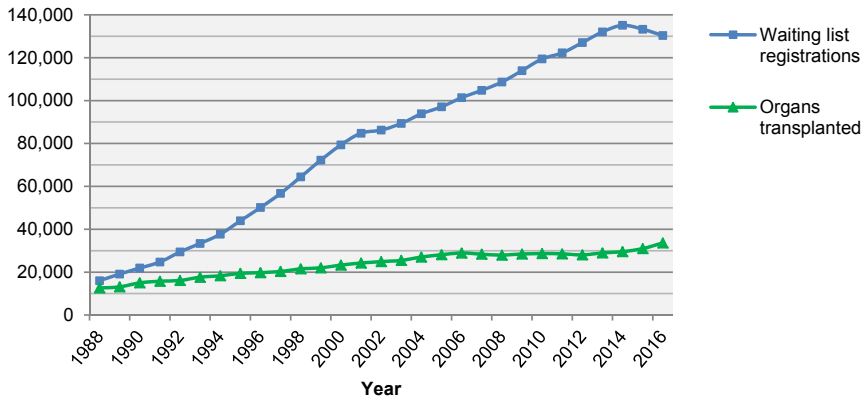

FIGURE 1-1 National transplant waiting list registrations for all organs (as of December 31 each year) and organs transplanted (living and deceased donors) by year.
SOURCES: Data from Eidbo, 2017; OPTN, 2017f.

TABLE 1-1
Waiting List Candidates by Organ Type as of July 13, 2017

Organ	Number of Waiting List Candidates
Total	117,154
Kidney	97,116
Liver	14,274
Heart	3,933
Kidney and Pancreas	1,708
Lung	1,352
Pancreas	905
Intestine	262
Heart and Lung	38

SOURCE: OPTN, 2017f.

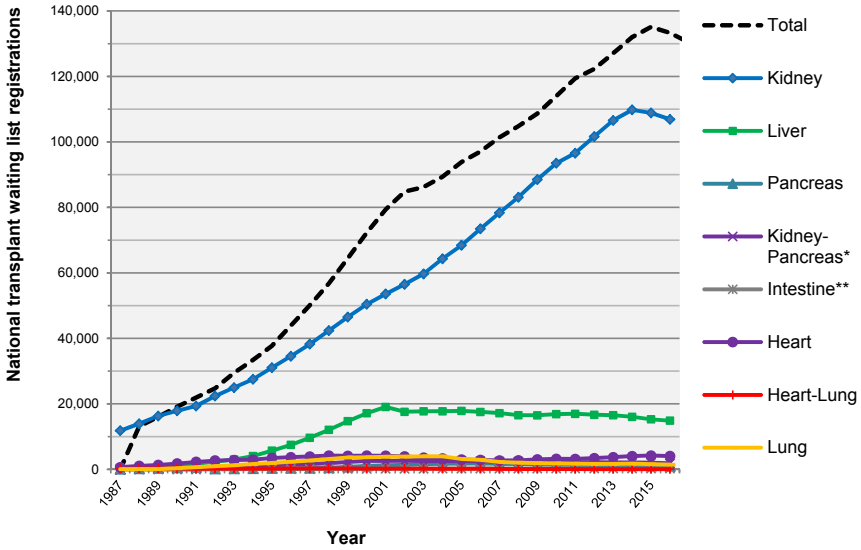

FIGURE 1-2 National transplant waiting list registrations, by organ, 1987–2016.
NOTES: Some candidates are wait listed with more than one transplant center, and therefore the number of registrations may be greater than the number of candidates. Waiting list totals are from December 31 each year from 1987 through 2016.

*A separate kidney-pancreas waiting list within the national transplant list was created in 1992.

**A separate intestine waiting list within the national transplant waiting list was created in July 1993.

SOURCE: Data from Eidbo, 2017.

physiological conditions prevent many potential donors from becoming actual organ donors.

Organ donor intervention research examines the interventions that are administered to a donor or to a donor's organs after death and after the authorization for donation has been granted by either the deceased donor (prior to death) or a surrogate. The intent of the research is to test interventions that are hoped to increase the likelihood of an organ being viable for transplantation and find ways to optimize graft function in organs that are transplanted into candidates.[1] For example, the quality of organs for transplantation might be improved with certain treatments carried out prior to organ recovery that transform organs that previously would not have been healthy enough for transplantation into organs that now are sufficiently healthy. Additionally, methods might be discovered that could increase the length of time that an organ is viable after recovery and before transplantation or that could reduce the time it takes until an organ reaches full or adequate function after transplantation. Examples of interventions that have been examined to date include hypothermia and varying perfusion solutions and processes (detailed in Chapter 3). The organs involved in this type of research are not used solely for research purposes—transplantation of the organ follows the research intervention. Thus, deceased organ donor intervention research has a dual purpose—furthering knowledge to improve outcomes and transplanting organs. However, deceased organ donor intervention research has not been extensively conducted to date because of the combination of the legal, regulatory, and ethical complexities associated with conducting this research and the inherent logistical complications that arise from the organ donation and transplantation process (Feng, 2010; Abt et al., 2013; Glazier et al., 2015; Heffernan and Glazier, 2017)—a process that requires decisions to be made in a short period of time by stakeholders (OPTN, 2017i).

STUDY BACKGROUND AND SCOPE

This report examines the ethical, legal, regulatory, policy, and organizational issues relevant to the conduct of research involving deceased organ donors. As will be further discussed throughout this report, a number of deceased organ donor intervention studies have already been conducted in which the donor organs were transplanted into organ recipients. However, because of the complexities of the organ donation and transplantation process—such as those that arise when one donor provides multiple organs that might be transplanted in different transplant centers across the United

[1] The committee for this study was not tasked with evaluating research on interventions administered after the transplant candidate has received an organ.

States—and because of the need to make decisions rapidly once organs become available, this type of research has proven challenging to conduct under the current U.S. policy and regulations regarding biomedical research (Abt et al., 2013; Glazier et al., 2015) (see Chapters 2 and 3).

In 2010, discussions about deceased organ donor intervention research began among a consortium of transplant organizations. These discussions resulted in work conducted by the Donor Intervention Research Expert Panel (DIREP) through the Organ Donation & Transplantation Alliance. DIREP examined the relevant issues and submitted its findings to the Health Resources & Services Administration in 2015 (Abt et al., 2015). Recommendations were also submitted to the Secretary of Health and Human Services (HHS) through the Secretary's Advisory Committee on Organ Transplantation.

On July 14, 2015, the National Academies of Sciences, Engineering, and Medicine (the National Academies) held a planning meeting to bring together interested individuals from professional associations, transplant programs, OPOs, foundations, federal agencies, and others to discuss the need for and scope of a potential study. The planning meeting participants determined that there was a need for a detailed and independent study to explore the complexities of deceased organ donor intervention research and recommend a path forward, and the planning meeting resulted in a draft scope of work for the study. In response, a group of sponsors—American Association for the Study of Liver Diseases, American Society of Transplant Surgeons, American Society of Transplantation, Association of Organ Procurement Organizations, Gift of Life Donor Program, Health Resources & Services Administration, Laura and John Arnold Foundation, National Institutes of Health (National Heart, Lung, and Blood Institute; National Institute of Allergy and Infectious Diseases; National Institute of Diabetes and Digestive and Kidney Diseases), National Kidney Foundation, OneLegacy Foundation, and The Transplantation Society—funded a National Academies study on organ donor intervention research.

To address the study statement of task (see Box 1-1), the National Academies appointed a 12-member committee with expertise in organ transplant surgery, organ procurement, pediatrics, decision science, law, ethics, clinical trial research, and organ donation public awareness and education efforts. Brief biographies of each of the 12 committee members can be found in Appendix B. The committee held four in-person meetings, with the first two having public sessions with invited speakers. The committee also held two public information-gathering conference calls. The agendas for the public meetings can be found in Appendix A. In addition, the committee reviewed the published scientific literature and considered

Box 1-1 STATEMENT OF TASK

An ad hoc study will examine the ethical, policy, regulatory, and organizational issues relevant to the conduct of research involving deceased organ donors (for purposes of the study, the concept excludes interventional research preceding declaration of death by neurologic or cardiopulmonary criteria among potential organ donors). The committee will examine the gaps, barriers, and opportunities for clinical research involving deceased donors that aims to increase the quality and quantity of donated organs available for transplantation, with particular attention to interventions administered to the donor and thus potentially affecting all of the donor's organs.

Specifically, the report will delineate the issues pertinent to organ donor intervention research and make recommendations that take into account public and professional trust in the organ donation process and ethical conduct of organ donor intervention research with attention to

- Ethical principles relevant to the conduct of interventional research on deceased donors and deceased donor grafts
- Responsibilities to donors and donor families
- Roles and responsibilities of donor hospitals
- Responsibilities to patients awaiting organs
- Responsibilities to transplant recipients of organs from donor intervention studies
- Delineation of ethical and regulatory oversight considerations specific to the safety of patients impacted by the study interventions (recipients of organs that were the target of the research intervention, and recipients of organs that were exposed to a research intervention but were not the targeted organs under study)
- Oversight and monitoring of organ donor intervention research, including addressing issues relevant to the type of review and oversight needed for
  - Evaluation of the scientific validity and potential efficacy of interventions in deceased donors to mitigate organ injury
  - Ethical framework for reviewing and evaluating conduct of clinical trials involving donor interventions
  - Evaluation of the impact on organ distribution with respect to waitlist morbidity and mortality
  - Review of the impact on transplant outcomes for all organs exposed to the intervention
- Impact on the distribution of research organs within the national system, and the implications for patients, health systems, investigators, donation professionals, organ procurement organizations, transplant professionals, and transplant centers

information and input provided by the public and various agencies and organizations. After having examined the complexities and challenges surrounding organ donor intervention research, the committee identified six goals to guide its work (see Box 1-2).

Box 1-2 GOALS IDENTIFIED BY THE COMMITTEE TO GUIDE ITS WORK ON ORGAN DONOR INTERVENTION RESEARCH

Goal 1: Improve transparency and public trust in the organ donation process for research followed by transplantation.

Goal 2: Improve the coordination and sharing of information about donor preferences.

Goal 3: Clarify legal guidance on organ donation for the purpose of research followed by transplantation (organ donor intervention research).

Goal 4: Promote informed consent for transplant recipients' participation in organ donor intervention research in a manner that is compatible with the logistical complexities of organ transplantation.

Goal 5: Establish centralized management and oversight of organ donor intervention research in order to ensure equitable, transparent, and high-quality research.

Goal 6: Promote transparency regarding organ donor intervention research and enable the implementation, tracking, and analysis of organ donor intervention research to improve transplantation outcomes.

OVERVIEW OF ORGAN DONATION AND TRANSPLANTATION

The process of organ transplantation begins with an authorization for organ donation. An individual's decision to be an organ donor may be designated at any point during his or her lifetime through an authorization to be listed as an organ donor on a registry through the department of motor vehicles (when applying for a driver's license or identification card) or through a state or national organ donor registry (see Chapter 3). The authorization for donation may also be made by a potential donor's family or other designated surrogate after death (see Chapter 3). (Living donation is not included in the statement of task and thus not discussed in this report.)

In deceased organ donation, as the term indicates, the organ removal occurs only after an individual has been declared dead. The determination of death can be made in two ways: (1) it can be based on the irreversible cessation of all functions of the brain, including the functions of the brain stem (i.e., neurologic determination of death); or (2) it can be based on the irreversible cessation of circulatory and respiratory function (i.e., circulatory determination of death) (see discussion later in this chapter). Deceased organ donors are more commonly declared dead by neurologic determination of death, although the number of donors declared dead by circulatory determination of death is rising each year (OPTN, 2017f) (see Table 1-2). This is because in cases of neurologic determination of death, organ viabil-

TABLE 1-2
U.S. Deaths Eligible for Organ Donation and Actual Donors, by Type, 2013–2015

Parameter	2013	2014	2015
Eligible deaths reported by DSAs[a]	9,173	9,258	9,781
Conversion rate (i.e., eligible deaths that become donors)[b]	71.2%	73.7%	72.1%
Deceased donors—neurologic determination of death	7,062	7,304	7,585
Deceased donors—circulatory determination of death	1,206	1,292	1,494
Total deceased donors	8,268	8,596	9,079

[a]OPTN/UNOS defines an eligible death as a death that meets established inclusionary criteria (e.g., neurologic determination of death, age 75 years or less) and without the presence of any exclusion criteria. Note that these inclusionary and exclusionary criteria vary by organ (OPTN, 2017b).

[b]Percentage of all eligible deaths that go on to become donors. The conversion rate uses donation service area (DSA) data and is calculated as the percentage of all eligible deaths that go on to become donors, after excluding all potential donors over 70 years of age and those deaths determined by circulatory criteria.

SOURCE: AOPO, 2017b.

ity can often be maintained through ventilatory support, thus increasing the likelihood of success for the transplantation. Donor-eligible deaths declared by neurologic determination of death are estimated to constitute 0.91 percent (9,793 deaths that were eligible for organ donation per the OPTN's definition of an eligible death) of the 1,072,828 deaths and imminent deaths in the United States referred to OPOs in 2015 (Israni et al., 2017).

Deaths determined by circulatory criteria often occur outside of the hospital or other medical facility. Organ donation after circulatory determination of death is possible, but there are often additional challenges to maintaining organ viability. These challenges include the delay between the cessation of circulatory and respiratory function and the recovery of organs for transplant, during which time the organs may be deprived of oxygen (Steinbrook, 2007). Efforts focused on increasing the potential for donation after circulatory determination of death continue to be implemented and further explored (Summers et al., 2015; Pabisiak et al., 2016; Wall et al., 2016; Jochmans et al., 2017; Miñambres et al., 2017; Scalea et al., 2017).

In the United States, organ donation and transplantation are accomplished through a cooperative, interdependent network of multidisciplinary, multi-institutional services. Oversight of this highly regulated process is coordinated by the federally mandated OPTN. UNOS operates the OPTN under a contract with the federal government. OPTN sets national policies for organ donation and transplantation which apply across all organizations involved in organ donation and transplantation—including OPOs, donor hospitals, and transplantation programs and centers (see Box 1-3).

Box 1-3 COMPONENTS OF THE ORGAN DONATION AND TRANSPLANTATION SYSTEM

Donation service area (DSA): A geographical area designated by the Centers for Medicare & Medicaid Services (CMS) for which an OPO and its designated transplant center(s) and donor hospital(s) are responsible for coordinating donations and transplantations. There are 58 DSAs within the United States (OPTN, 2017b).

Donor hospital: A hospital that is contracted to work with its assigned OPO to facilitate the recovery of donor organs and tissues. Donor hospitals must abide by the regulations outlined in the Conditions of Participation for Hospitals Regarding Organ, Tissue and Eye Donation, which requires hospitals to promptly report all deaths to their OPO, establishes the OPO as the determiner of medical suitability for donation, and establishes the OPO or trained staff, rather than hospital staff, as the sole requesters of authorization for donation.[a]

Organ Procurement and Transplantation Network (OPTN): The OPTN is a public–private partnership established by the National Organ Transplant Act in 1984 to bring together the key stakeholders to develop policies and maintain the regulatory framework of the organ donation and transplantation system, with the goal of increasing the availability of organs and the accessibility of transplantations, improving health outcomes, and ensuring participant safety (OPTN, 2017a).

Organ procurement organization (OPO): There are 58 OPOs in the United States and each is responsible for the provision of donation and donor management services within its DSA. These organizations are certified by CMS and are mandatory members of the OPTN. In addition, OPOs actively work to educate the public about organ donation and to increase donor registrations (HRSA, 2017).

As detailed in Table 1-3, there are 58 OPOs responsible for procuring and distributing organs to 254 transplant centers. Different programs within these hospital centers are responsible for the transplantation of specific organs and the follow-up care for organ transplant recipients.

Additionally, 152 histocompatibility laboratories are responsible for conducting pre-allocation donor and recipient histocompatibility testing, and there is an extensive national computerized network used to match donated organs with potential recipients (UNOS, 2015c; OPTN, 2017e).

The network operates in units referred to as donation services areas (DSAs). Each DSA encompasses one OPO, the donor hospitals contracted to work with the OPO, and the assigned transplant hospitals, transplant programs, and histocompatibility labs that serve the service area. The 58 DSAs are geographically and culturally diverse (see Figure 1-3) and work within the nation's 11 transplant regions.

Scientific Registry of Transplant Recipients (SRTR): The SRTR is operated under a competitively awarded contract from the Health Resources & Services Administration (HRSA). The registry is responsible for providing analytic and evaluation support to the OPTN and the U.S. Department of Health and Human Services, including policy evaluation, report preparation, and analysis of performance metrics (SRTR, 2017).

Transplant center: A medical center approved by CMS to carry out transplantations in coordination with its designated OPO as well as to coordinate the registration of transplant patients on the waiting list and to provide medical care before and after the transplant. The transplant center is required by CMS to promptly provide data to OPTN on all transplants performed.[b]

Transplant program: A unit within a CMS-approved transplant center that specializes in the transplantation of a specific type of organ or tissue (CMS, 2013).

United Network for Organ Sharing (UNOS): UNOS is a private, nonprofit organization that since 1986 has contracted with HRSA to operate the OPTN. UNOS is responsible for the day-to-day function of the donation and transplantation system, including the management of the waiting list and organ allocation process, maintenance of the transplantation database, verification that allocation practices are in line with policy guidelines, and encouragement of public education about the importance of organ donation (UNOS, 2015a).

[a]42 C.F.R. § 482.45.
[b]42 C.F.R. Part 482.

DSAs act as semi-autonomous units. Historically they worked to procure and transplant organs locally, that is, within their DSA. However, because of recent advances in transplantation science and in efforts to reduce geographic disparities, changes have been made to the organ allocation system so that allocation increasingly functions on a more national scale—which is managed by OPTN/UNOS—and therefore organs can be shared across DSA boundaries (Davies et al., 2017; OPTN, 2017j).

Because the demand for donor organs exceeds the supply, individuals who need an organ transplant must be placed on a waiting list for the type(s) of organ they need. Criteria for being placed on the waiting list and the amount of time spent waiting on the list prior to receiving a transplant differ depending on the type of organ needed and the DSA in which the donor is waitlisted (Davis et al., 2014; Davies et al., 2017; OPTN, 2017j). An extensive discussion of the reasons for these differences is beyond the

TABLE 1-3
OPTN Members and Transplantation Statistics

UNOS Region	1	2	3	4	5	6	7	8	9	10	11	Total
OPOs[a] (DSAs)	2	5	10	4	8	3	4	5	4	6	7	58
Transplant centers[a]	14	35	31	31	33	9	22	20	16	20	25	254
Histocompatability laboratories[a]	10	18	16	16	23	4	15	9	11	13	17	152
Transplant procedures performed using organs from deceased donors[b]	1,116	3,454	3,995	2,867	4,608	885	2,232	1,703	2,386	1,631	2,753	27,630

NOTES: Seven OPTN members operate both transplant centers and in-house OPOs, and 97 operate both transplant centers and in-house histocompatibility laboratories. DSA = donation service area; OPO = organ procurement organization; OPTN = Organ Procurement and Transplantation Network.

[a]Data as of July 13, 2017.

[b]2016 data.

SOURCES: OPTN, 2017e,f.

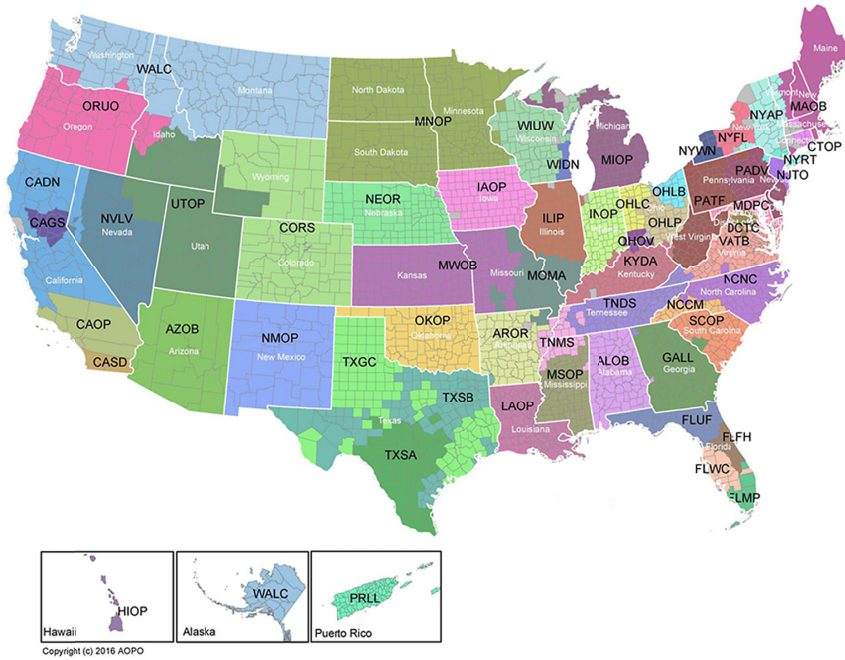

FIGURE 1-3 Donation service areas, 2016.
SOURCE: AOPO, 2017a. Reprinted with permission from AOPO.

scope of this report, but, in brief, waiting list criteria were developed with the goal of ensuring that donor organs are used optimally (i.e., in such a way as to minimize death among transplant candidates on the waiting list) and that they are allocated in an ethical, fair, and equitable manner. Thus, for each organ the candidates on the waiting list who are medically able to receive a transplant and who are at the greatest risk of dying without a transplant are given priority (UNOS, 2015b). Factors associated with dying from end-stage organ failure differ among organs. Therefore, the criteria used to objectively determine priority to receive a transplant vary depending on the organ in question (OPTN, 2017i). For example, patients suffering end-stage kidney disease can be supported by dialysis for extended periods of time. However, despite recent improvements, the 5-year survival of patients with end-stage kidney disease remains low when compared to survival following deceased donor transplant, 42 percent versus 76 percent, as of 2009 (Saran et al., 2017). Hence, the time spent on the waiting list is one of the most decisive factors in determining patient priority to receive a donor kidney (OPTN, 2017i). On the other hand, for patients

with end-stage liver disease—who have no therapeutic options that can replace liver function—a patient's risk of dying is calculated using physiologic parameters, and this calculated risk is used to determine the patient's priority to receive a donor liver (OPTN, 2017i). Even with these efforts to prioritize the most dire cases, thousands of patients die each year for want of a donor organ.

The 58 OPOs in the United States are responsible for obtaining and verifying authorizations for organ donations and for working with donor hospitals to procure and allocate organs from deceased donors. Depending on the condition of the deceased donor and the donor's organs, an individual can donate up to eight solid organs (two kidneys, the pancreas, the heart, two lungs, the intestines, and the liver) which can be transplanted into eight or—if the liver and lungs are subdivided—even more recipients. In the time between the declaration of the donor's death and the procurement of the donor's organs, the authorized OPO and donor hospital implement donor management protocols that include administering medications, maintaining the deceased donor's body at a particular temperature, and various other actions, all taken with the intent to maintain the organs in the best condition possible by minimizing organ stress, damage, and dysfunction until the organs are recovered (McKeown et al., 2012; Kotloff et al., 2015; Kumar, 2016).

If research followed by transplantation (organ donor intervention research) has been authorized, the research intervention would be administered to a deceased donor prior to organ recovery or to the target organ after the organ has been recovered but before transplantation. When the research intervention is administered prior to organ recovery and the intent is to have an effect on a specific organ (i.e., the target organ), the intervention could affect other organs from the same donor that may also be removed and transplanted after the intervention (i.e., non-target organs). As a result, many transplant recipients across multiple transplant centers could become human subjects in a single organ donor intervention research study.

The goals of such research are to improve the quality and increase the quantity of organs for transplantation—and, specifically, the intent of this research is to identify interventions that will allow the maximum number of transplantable organs to be recovered in a condition that will result in the best possible organ graft function in the recipient.

When an organ becomes available and a potential recipient is identified through the allocation process, the potential recipient's transplant team is notified and provided with details about the organ. If the transplant team determines that the organ is acceptable, it will contact the potential recipient to determine his or her current state of health and interest in proceeding with the transplantation. In order that the organ be maintained in optimal condition, the decision of whether to accept an organ offer and move

forward with transplantation needs to be made quickly—usually within 1 hour of receiving the offer and accessing the deceased donor's information (OPTN, 2017i)—and the transplantation surgery proceeds as soon as possible after the organ is accepted and received.

After transplantation, patients receive extensive follow-up care. Transplantation and follow-up data are submitted by transplant programs to OPTN/UNOS and analyzed by the Scientific Registry of Transplant Recipients (SRTR). OPTN/UNOS and SRTR make the de-identified data available to the general public, clinicians, researchers, policy makers, and regulatory agencies. The data can be accessed by searching in multiple ways including by transplant program, recipient and donor demographics, the number and type of transplants performed, and the outcomes for organ grafts and transplant recipient survival within the first year after transplant.

Although practices vary by OPO, OPTN has issued broad guidance on the routine sharing of standard information and the coordination of communication between donor families and recipients. Communication following transplantation is largely dependent on the wishes of the donor's family, who can receive information about which organs were transplanted and certain non-identifying information about the recipient (e.g., whether the recipient was young or old, whether the transplant was lifesaving, etc.). According to the guidance, recipients may express their gratitude through notes that are reviewed by and exchanged through the OPO to donor families, if they are receptive, and donor families may respond (OPTN, 2012).

TERMINOLOGY

Organ donation and transplantation elicit heightened sensitivities from the public. Because deceased organ donation involves the death of one human being resulting in the gift of one or more donor organs to one or more transplant candidates, the transplantation process is closely intertwined with the emotions that surround death and dying. Furthermore, organ donation and transplantation depend on upholding the public's trust.

The committee carefully considered the terms used in this report and emphasizes—as do others in the donation and transplantation community—that the terms used to describe and the depiction of organ donation and transplantation need to be clear, accurate, transparent, and respectful. Honoring the donation and reflecting the high scientific rigor of this process are critical.

For this study, the terms used in discussing deceased donation are particularly relevant. Organ donor intervention research occurs after the determination of the donor's death. Death is determined using neurologic or cardiac and respiratory criteria. *Neurologic determination of death* refers to the determination of death by irreversible cessation of all functions of the

brain including the functions of the brain stem. *Circulatory determination of death* indicates a determination of death made by observing the irreversible cessation of cardiac and respiratory function (i.e., the heart and lungs and other circulatory system components cease to function) (Bernat et al., 2006). The term "brain death" is sometimes used in cases where there is a neurologic determination of death, but the term is not entirely accurate because the declaration of death described in this manner does not account for the possibility of some remaining functions such as anterior pituitary neurohormonal regulation (Halevy and Brody, 1993).

The terms used to describe the removal of the organs from the deceased individual have evolved over time (IOM, 2006). Although the term "harvest" is no longer generally accepted or used because there is an impersonal nature to the word in the context of organ donation and because it has a largely agricultural context, it can still be heard occasionally. Similarly, the term "retrieve" may have an impersonal connotation. More generally accepted terms include "recover" or "receive" to highlight the gifting of the organ. The term "procure" is often used and has a transactional meaning, but more personal terms might be preferred. This report uses the terms "recover" and "procure."

As noted throughout this report, one of the major challenges for organ donor intervention research is that an intervention conducted in the deceased donor's body to improve the viability of one organ for transplantation (the target organ) may affect other organs (non-target organs). The term "non-target organs" focuses on the intent of the specific intervention. The term "bystander organs" has also been used, but the committee determined that this is less helpful as it suggests non-involvement or "observer" status rather than the potential to be impacted. Much remains to be learned about the impact of research interventions in deceased donors on the non-target organs.

There is debate about the best terms to use for an individual's decision to donate his or her organs after death. The available literature and public policies use several of the following: "donation," "consent to donation," "authorization for donation," "donor authorization," "make an anatomical gift," "become an organ donor," "register as a donor," "agree to donate," etc. While each of these may be useful in some contexts, this report gives priority to the term "authorization," both for the decedent's prior decision to donate his or her organs and for the surrogate's decision to donate those organs in the absence of the decedent's prior decision. Not only is "authorization" now widely used with strong support in UNOS and elsewhere, but it can help avoid confusion in this report which also discusses consent for participation in research involving human subjects. The committee affirms what was previously said in the 2006 Institute of Medicine report: "As terms continue to evolve, the committee urges all who

are involved in organ transplantation to use words and phrases that clarify rather than mystify the process of organ transplantation and that affirm the value of each individual human life" (p. 31).

CONTEXT FOR THIS STUDY

Organs That May Pose Additional Risk for a Transplant Recipient

To ensure that potential recipients understand characteristics of donated organs that may impact their transplantation outcomes, policies have been developed to inform potential recipients about organs from donors that may have risks differing from those of the general population of deceased organ donors. The two categories, which vary based on requirements for informed consent and type of risk to the recipient, are *expanded-criteria donors* and *increased-risk donors*.

Expanded-Criteria Donors

Characteristics of some types of donors—for example, older age, circulatory determination of death, or biological measures above preferred thresholds—have been identified as being associated with a greater likelihood of the donated organ having poor function following transplantation (Rao and Ojo, 2009). Deceased donors who have characteristics that do not meet the OPTN/UNOS definition of an eligible death can be referred to as *expanded-criteria donors*.[2]

Current OPTN policy language defines a death as eligible for donation if the potential donor is age 75 years or less, declared dead by neurologic criteria, has at least one organ that meets organ-specific eligibility definitions, meets all other inclusionary criteria (weight, body mass index, etc.), and does not present with any exclusionary criteria. Some general exclusionary criteria include death from specific causes (e.g., certain cancers) and presence of certain infections (e.g., tuberculosis) (OPTN, 2017h). In terms of organ specific definitions, a kidney would be considered to not meet the OPTN definition of an eligible death if the potential donor is over 70 years of age or has a creatinine level of greater than 4.0 mg/dL. Additionally, a heart would not meet the definition if the potential donor is older than 60 years of age or has had a myocardial infarction (OPTN, 2017h). It should be noted that the OPTN definition of an eligible death is used by DSAs for reporting purposes and does not bar an OPO from moving forward with a donation from a potential donor (OPTN, 2017h). For

[2]Kidneys are now classified using the "kidney donor profile index" rather than "expanded criteria donor," a discussion of which is beyond the scope of this report.

example, in 2016, 2 hearts were transplanted from donors over the age of 65 years and in that same year 3,246 organs were transplanted from circulatory determination of death donors (OPTN, 2017f).

Concerns about the quality of expanded criteria donors or about particular donated organs result in many potential donors and donor organs being turned down for transplantation each year. Expanded-criteria organs can carry an increased risk of graft failure, dysfunction, or disease transmission (Rao and Ojo, 2009; Feng and Lai, 2014). However, such organs may provide better long-term health outcomes for a recipient than would be expected from not receiving an organ transplant at all (Doshi and Hunsicker, 2006; Rao and Ojo, 2009). Recent expansion of the criteria for acceptable kidney transplantation has allowed the transplant of a number of kidneys that previously would not have been recovered from the donors (Wynn and Alexander, 2011). Developing novel and innovative interventions that improve the outcomes for expanded criteria donor organs offers a significant opportunity to improve the quality and increase the number of deceased donor organs suitable for transplantation.

Increased Risk Donors

Deceased donors who have certain characteristics that increase the risk of transmission of an infectious disease to the recipient are classified by the U.S. Public Health Service (USPHS) as increased risk donors. In 2013, the USPHS published guidelines for the assessment and testing of organs from donors at increased risk for HIV, hepatitis B, and hepatitis C (HCV)—all deceased donors are now tested for these diseases prior to organ recovery—and established a process for obtaining informed consent, a requirement for the use of increased risk organs, from transplant candidates who choose to accept these organ offers (Seem et al., 2013). The OPTN Ad Hoc Disease Transmission Advisory Committee released a guidance document on how to communicate with potential recipients regarding increased-risk donor organs (OPTN, 2017c). Beyond the increased risk classification for donors, researchers have recently explored the safety and efficacy of kidney transplantation from confirmed HCV positive donors to HCV negative recipients, followed by antiviral therapy for the recipient post-transplant as a strategy to expand the donor pool (Reese et al., 2015; Goldberg et al., 2017).

The HIV Organ Policy Equity (HOPE) Act legalized the transplant of organs from HIV-positive donors into HIV-positive recipients, in the setting of clinical research.[3] On November 21, 2015, the Secretary of HHS finalized the OPTN standards of quality for the recovery and transplantation

[3]HIV Organ Policy Equity Act, Public Law 113-51, 113th Cong. (November 21, 2013).

of organs from HIV-positive donors as required by the HOPE Act. The Secretary also published criteria for research relating to the transplantation of organs from HIV-positive donors into HIV-positive recipients, allowing the HOPE Act to take effect. The research criteria specify that organs from individuals infected with HIV may be transplanted only into individuals who are infected with HIV before receiving such organs and who are participating in clinical research approved by an institutional review board (*Federal Register*, 2015).

Organs Determined to Be Unsuitable for Transplantation

Despite the long waiting lists for donated organs, every year some organs that are recovered for use in transplantation are subsequently determined to be unsuitable for this purpose (see Figures 1-4 and 1-5 and Table 1-4). Some of the reasons for making this determination include disease, injury to the organ, and the elapse of too much time between recovery and transplantation (Israni et al., 2017).

Many organs that are recovered from deceased donors for transplantation, but not transplanted are used for research purposes (i.e., research that is not followed by transplantation). In some cases these organs are known prior to recovery to be unsuitable for transplantation but often they are determined to be unsuitable only after recovery. In both types of cases, some of the recovered organs may be useful for research purposes (see Table 1-5), while others will not be useful for research or any other purpose (e.g.,

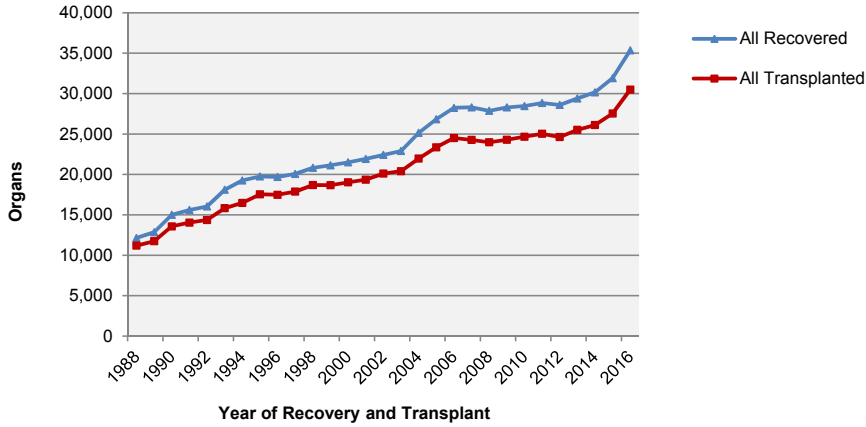

FIGURE 1-4 Number of deceased donor organs that were recovered compared with the number that were transplanted, 1988–2016.
SOURCE: Data from OPTN, 2017f.

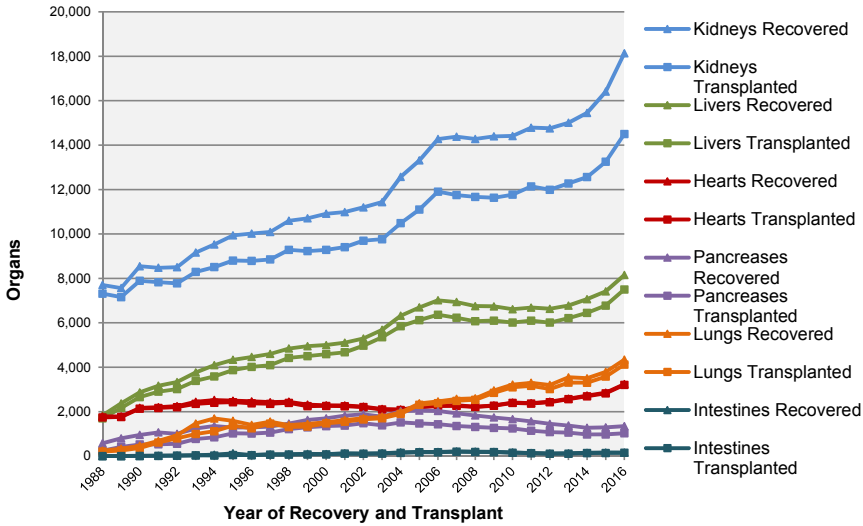

FIGURE 1-5 Number of deceased donor organs that were recovered compared with the number that were transplanted, by type, 1988–2016.
SOURCE: Data from OPTN, 2017f.

TABLE 1-4
Organs from Deceased Donors Discarded in 2016, by Type

Organ	Number
Intestines	8
Hearts	31
Lungs	221
Pancreases	320
Livers	741
Kidneys	3,631
Total discarded	4,952

NOTE: This table does not include the number of organs from authorized donors that were never recovered for transplant. Please see Figures 1-6, 1-7, and 1-8 for more detail.

SOURCE: OPTN, 2017f.

TABLE 1-5
Recovered Organs Used for Research Purposes, 2013–2015

Parameter	2013	2014	2015
All deceased donors	8,268	8,596	9,079
Organs recovered for transplant but ultimately submitted to research	811	1,067	1,080
Organs recovered for research purposes	3,265	4,214	4,549
Total research organs	4,076	5,281	5,629

NOTE: Data are not available to delineate organs that were used in a research capacity and that were later transplanted.

SOURCE: AOPO, 2017b.

education). With nearly 5,000 organs discarded from deceased donors in 2016 alone (see Table 1-4), there is the potential to perform more transplant surgeries and save more lives if new methods to improve organ quality and preservation can be developed. Such opportunities for developing these new methodologies could also exist by utilizing unused organs, those organs that are currently not recovered for transplant. Organ donor intervention research presents an opportunity to discover methods to improve organ quality and viability. Figures 1-6, 1-7, and 1-8 provide three examples (left kidney, heart, and liver, respectively) illustrating how some organs were used after recovery in 2015. Some of the areas in which organ donor intervention research may have a substantial impact are in those organs that are not transplanted because of poor organ function, vascular damage, and organ trauma. While there will continue to be organs that are not suitable for transplantation, reducing that number is a goal worth pursuing.

Time Constraints in the Organ Donation and Transplantation Process

After an organ is recovered from a donor, there is a window of time during which the organ can be preserved; once this window passes, the organ can no longer be reliably counted on to function adequately after transplantation. The length of preservation time varies by the organ type (see Table 1-6). Several activities must occur during this window of time, including (1) the allocation of the organ to a transplant candidate; (2) the offer to and acceptance of the organ by the transplant candidate and the transplant team; (3) admission of the transplant candidate to the hospital, which may be complicated by a candidate's lack of proximity to the hospital; (4) transporting the organ from the donor's hospital to the transplant

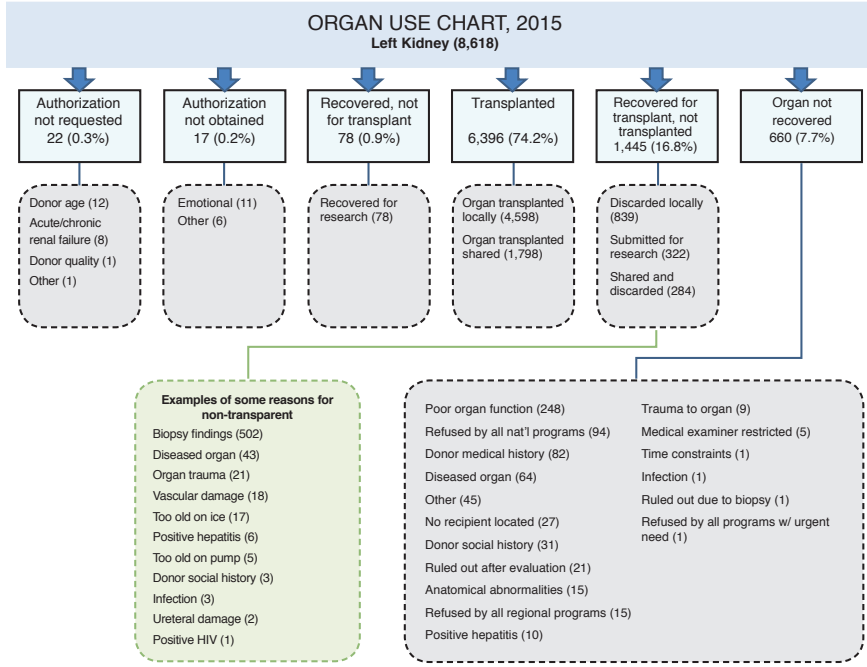

FIGURE 1-6 A summary of authorization, recovered, transplanted, and discard status of deceased donor left kidneys in 2015.
SOURCE: Adapted from Israni et al., 2017.

candidate's hospital; (5) obtaining clinical consent from the transplant candidate for surgery, and pre-operative evaluation of the transplant candidate; and (6) pre-operative preparation of the candidate. Hence, a transplant candidate and his or her transplantation team have only a short period of time during which to decide whether to accept a given organ, particularly if the organ is a heart or a lung.

Geographic Disparities in Organ Allocation

Because of past challenges in transporting organs and maintaining their viability, until recently the organ allocation system has focused primarily on local or regional allocation. However, there has been some discussion about the division of regions for particular organs because some regions have longer waiting lists than others do. For instance, the waiting list for a liver in Massachusetts is much longer than the waiting lists in Florida and

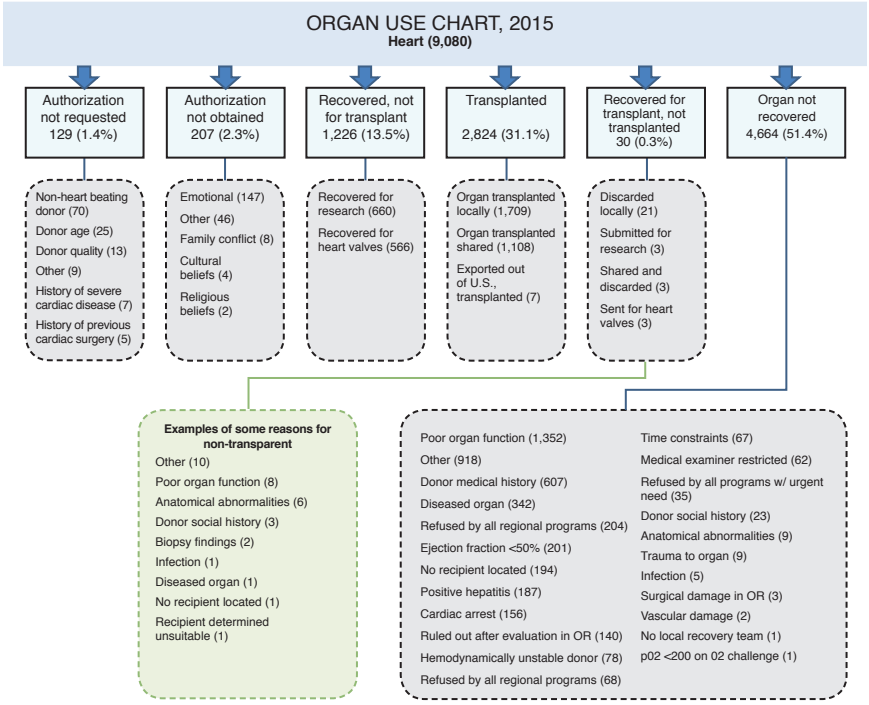

FIGURE 1-7 A summary of authorization, recovered, transplanted, and discard status of deceased donor hearts in 2015.
NOTE: OR = operating room.
SOURCE: Adapted from Israni et al., 2017.

South Carolina because the supply of organs in the latter states is greater relative to the number of transplant candidates on the waiting lists (Ladin et al., 2017). Ladin and colleagues (2017) proposed that this may be due in part to such factors as the residents of Massachusetts having greater access to health care and fewer deaths that would increase the organ supply (e.g., from motor vehicle accidents).

For some organs there is now the possibility of moving toward allocation algorithms that prioritize candidates across the country rather than those who are local to the location of the deceased donor. Allocation policies are being reviewed to balance the goal of creating a more equitable system with the goal of promoting efficiency. For example, OPTN is evaluating changing geographic boundaries for the allocation of livers (OPTN, 2017j); however, this has been met with controversy (Kowalczyk, 2016; Naugler, 2016; OPTN, 2016, 2017j) and remains a topic of ongoing discussion (OPTN, 2017g).

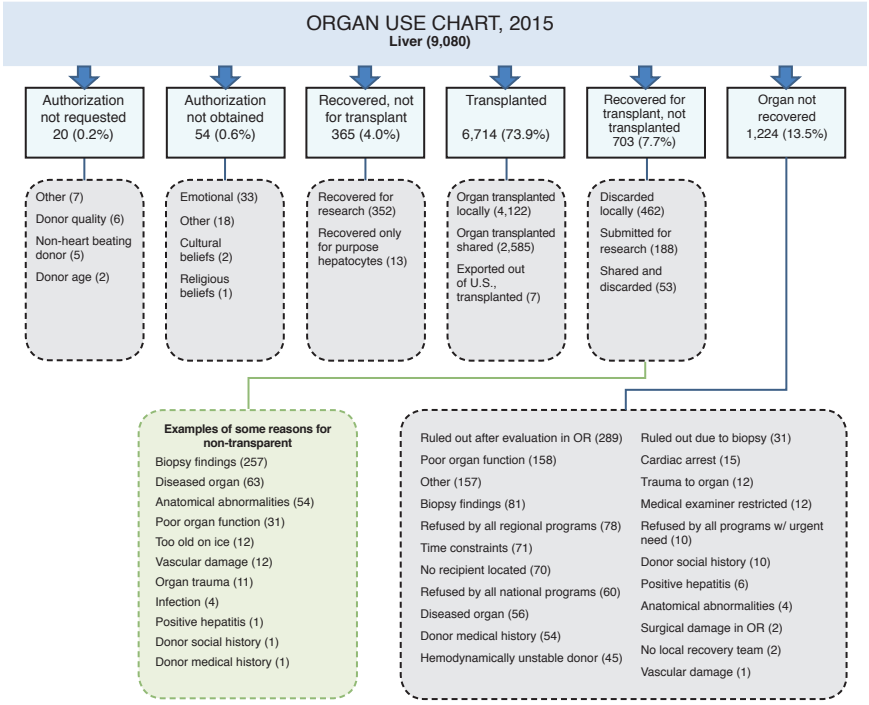

FIGURE 1-8 A summary of authorization, recovered, transplanted, and discard status of deceased donor livers in 2015.
NOTE: OR = operating room.
SOURCE: Adapted from Israni et al., 2017.

TABLE 1-6
General Maximum Preservation Time, by Organ

Organ	Preservation Time
Heart and lungs	4 to 6 hours
Liver	8 to 12 hours
Pancreas	12 to 18 hours
Kidney	23 to 36 hours

SOURCE: OPTN, 2017d.

DISTINGUISHING RESEARCH FROM QUALITY IMPROVEMENT STUDIES

The focus of this report is on research—specifically, deceased organ donor intervention research. However, the committee recognized that improvements in donor management have frequently resulted from quality improvement (QI) studies and noted that there is ongoing discussion about the boundaries between quality improvement and research in this field, as in many areas of clinical medicine (Casarett et al., 2000; Baily et al., 2006). QI and research are the two fundamental processes used to improve clinical practice, and organ donor management and transplantation efforts are already enmeshed with innovative procedures, formal research protocols, and the introduction of new interventions with deceased donor organs that fall somewhere on the spectrum between quality improvement and translational research.

What constitutes research versus quality improvement? Definitions that have been used for each term highlight some of the characteristics that can be used to differentiate QI from research:

- *Quality improvement:* "systematic, data-guided activities designed to bring about immediate, positive changes in the delivery of health care in particular settings" (Baily et al., 2006, p. S5).
- *Research:* "systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."[4]

Casarett and colleagues distinguished the two terms based on "if (a) whether the majority of patients involved are not expected to benefit directly from the knowledge to be gained, and (b) if additional risks or burdens are imposed to make the results generalizable" (2000, p. 2275). QI studies are often used to address deficiencies and disparities in the provision of health care by developing protocols, checklists, and other morbidity reducing measures to identify and implement morbidity reducing measures or to put protocols in place to adhere to standards of care and best practices (Howard et al., 2007; HRSA, 2011; Seoane et al., 2013).

The goals of QI and research differ. QI uses data-guided testing that is designed to bring about immediate improvements in the delivery of clinical care. QI activities take place in a continually changing environment and may be simply considered good clinical practice combined with systematic, experiential learning (Davidoff et al., 2008).

[4] 45 C.F.R. § 46.102.

On the other hand, the goal of research is to conclusively test the effectiveness and safety of interventions through a convention of rigorous systematic investigation—most commonly, randomized controlled trials. As noted by Baily and colleagues (2006),

> Allowing research subjects to assume the burdens and risks of research is justified by the expectation of societal benefits from the new knowledge produced; publication is an important step in conveying the new knowledge to those who can put it into practice and thereby create the social benefits. Although the [HHS] definition does not make it explicit, the regulations implicitly reflect a view of research as a knowledge-seeking enterprise that is independent of routine medical care. (p. S11)

Attention to this issue is particularly pertinent to the field of organ donor intervention studies because of the potential impact an intervention may have on multiple individuals at multiple medical facilities and given the priority of ensuring that appropriate human subjects research protections are in place. In Chapter 4 the committee discusses this issue further with regard to the oversight of organ donor intervention studies.

CHALLENGES AND OPPORTUNITIES IN ORGAN DONOR INTERVENTION RESEARCH

Deceased organ donor intervention research offers an opportunity to gain the knowledge needed to maximize the benefits of the gifts of donated organs. This research involves challenges that are both similar to and different from other forms of clinical research (see Box 1-4). The committee's work focused on identifying next steps in overcoming these challenges so that research can be conducted that will improve the quality and increase the quantity of organs available for transplantation. This research is a critical component within a range of ongoing initiatives and not yet fully tapped opportunities—including public education efforts, organ donor registry and policy and regulatory changes—that have the potential to further increase organ donation and opportunities for transplantation and, as a result, to improve the health and well-being of many individuals.

ORGANIZATION OF THIS REPORT

This report covers the breadth of the committee's statement of task. Chapter 2 outlines the ethics principles—respect for persons, beneficence/utility, fairness, validity, and trustworthiness—that are the basis for moving forward with organ donor intervention research. In Chapter 3 the committee explores the legal, regulatory, and policy framework for organ

Box 1-4 CHALLENGES IN DECEASED ORGAN DONOR INTERVENTION RESEARCH

Features That Can Be a Challenge Across All Fields of Clinical Research

- Multi-site trials
- Differentiating between quality-improvement studies and research studies
- Implementing appropriate levels of oversight and protections for human subjects
- Ensuring that potential participants understand the risks, benefits, and alternatives to participating in research
- Delineating consensus on standards of practice
- Limited funding sources and resources

Challenges Unique to Deceased Organ Donor Intervention Research

- Multiple individuals—Research conducted in the deceased donor being assessed in the recipient(s)
- Non-target organ recipients—Research intervention on the target organ may have impacts on other organs
- Unknown at the outset of the research who will be involved in the research study:
  - Numerous potential organ recipients
  - Numerous OPOs, donor hospitals, and transplant centers
- Rapid decision making required for the transplant program and the potential recipient
- Recent changes in the organ allocation system to move from a local and regional focus to a national approach
- Guidelines for research may interact with the guidelines for allocation in such a way that the distribution of the organs is altered, so it is possible that some transplant candidates might wait longer to receive an organ than they would in the absence of research

donation and research participation relevant to organ donor intervention research and sets forth its recommendations for interpreting, applying, and in some instances, revising that framework. The report concludes in Chapter 4 with the rationale and structure for centrally administered oversight of this research focusing on the essential functions needed to maintain and sustain the integrity and trustworthiness of the nation's organ donation and transplantation system.

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2

Ethical Framework

The ethical principles presented in this chapter support the committee's working assumptions that organ transplantation is a good that is worth pursuing and expanding and that it is thus important to increase the number and improve the quality of organs for transplantation in order to save lives and improve recipients' quality of life. A close analysis of these principles—and the legal, regulatory, and policy frameworks that to some extent embody them—indicates several conditions under which organ donor intervention research as a way to improve and increase organs available for transplantation can be both ethically justified and ethically conducted. In discharging its task to examine "ethical principles relevant to the conduct of interventional research on deceased donors and deceased donor grafts" (see Chapter 1), the committee sought to illuminate the responsibilities of various agents—to the donors and donor families/surrogates, to candidates for organ transplantation, and to the recipients of organs from such research (both recipients of research-targeted organs and of non-target organs).

To identify and elucidate the relevant ethical principles for assessing and guiding the policies for and practices of organ donor intervention research—research that is at the intersection of organ donation and research involving human subjects—it is useful to examine "current practices, policies, laws, opinion surveys, and cultural and religious traditions as interpreted by the spokespeople for relevant organizations and other experts (e.g., philosophers, theologians, anthropologists, and sociologists)" (IOM, 2006, p. 77). While there are diverse views, there is a rough consensus concerning several ethical principles.

This rough consensus is evident in the work of several interdisciplinary groups that have, with public input, attempted to formulate principles for the spheres of activity that are central to the current committee's work. For instance, in 1979 the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued the *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). Moreover, in 2015 the Ethics Committee of the United Network for Organ Sharing (UNOS) updated an earlier white paper entitled *Ethical Principles in the Allocation of Human Organs* (OPTN, 2015).[1] While focused on the allocation of donated organs, this white paper presents principles that are also applicable to recovering deceased donor organs: "The principles involved are essentially the same as those that apply to other areas of human conduct, . . . reflect the conclusions of American public bodies which have examined general principles of ethics . . ., [and in] slightly different language . . . are essentially the same as those that appeared in the Belmont Report"[2,3] (OPTN, 2015).

Ethical principles are often embodied and embedded in laws, regulations, and policies. A good example is the Uniform Anatomical Gift Act (UAGA), some version of which guides the transfer of organs from deceased persons in each state, the District of Columbia, and Puerto Rico (Organ Donation & Transplantation Alliance, 2017). Another good example is the Federal Policy for the Protection of Human Subjects (also termed the Common Rule), which is the core federal policy that governs federally funded and much privately funded research involving human subjects in the United States.[4] Each of these incorporates and seeks to balance several principles.

[1]This white paper does not represent Organ Procurement and Transplantation Network (OPTN) policy but is rather intended to provide information and to stimulate public discussion (OPTN, 2015). See also the OPTN Ethics Committee's white paper *Ethics of Deceased Organ Donor Recovery* (OPTN, 2016).

[2]A footnote in this white paper emphasizes that these same principles appear in different wording in a number of books in bioethics and transplantation ethics. It identifies "alternative formulations of essentially the same list of principles" in Beauchamp and Childress (2013) and Veatch and Ross (2015) (OPTN, 2015). The white paper's emphasis on the essential "sameness" of the principles, despite varied formulations, can be maintained only if it is also recognized that there are different interpretations of the meaning, scope, and weight of these principles in concrete situations.

[3]The rough consensus concerning several ethical principles does not mean that each public body simply adopts, adapts, and applies that consensus. Reflecting on the work of the Presidential Commission for the Study of Bioethical Issues, commissioner Daniel Sulmasy (2017) contends that this commission's principles, similar though they are to the *Belmont Report*'s principles, emerged more inductively as the commission sought to address the issues raised by synthetic biology.

[4]45 C.F.R. 46.

Nevertheless, ethical principles usually also go beyond the laws and regulations that attempt to embody them.

- Some ethical principles may entail actions that are not mandated by laws and regulations;
- Some may fill in gaps where laws and regulations are incomplete or indeterminate; and
- Some may provide reasons to criticize and revise laws and regulations, especially as technological and social conditions change.

The last occurred both with the UAGA in its revisions since the original 1968 version and with the Common Rule in its 2017 revision (to take effect in 2018). The Notice of Proposed Rule Making for the Common Rule indicated that the recommended revisions had resulted from reassessing the core ethical principles in the context of current technological and social changes, and it requested public comment on "whether the proposals strike a reasonable balance among the core ethical principles. A better balance among the core principles should increase the strength of the partnership between the research enterprise and the public" (*Federal Register*, 2015, pp. 53941–53942).

Even within a rough consensus about several ethical principles, differences may arise in the interpretations of what these principles imply for establishing or revising laws, regulations, policies, or practices. Rarely does anyone claim that the principle of respect for persons, for instance, is irrelevant to organ donation/transplantation or to research involving human subjects, but different interpretations of its range of application and its weight may thwart agreement on what this principle implies for specific projects. As such, appeals to this principle (or to other principles) do not automatically produce unanimous judgments about complex practices such as organ donor intervention research. Much depends on developing a clear understanding of this research, of what is required for it to succeed, and of how various options in its pursuit might fulfill these principles. With this understanding, determining whether organ donor intervention research can be ethically acceptable under certain circumstances requires close attention to the relevant ethical principles as well as to the applicable legal, regulatory, and policy frameworks that represent, even if imperfectly, attempts to embody those principles. This chapter explicates several relevant ethical principles; the next chapter will delve more deeply into these frameworks.

ETHICAL PRINCIPLES

The ethical principles most relevant and important for the committee's task are respect for persons, beneficence, fairness, validity, and trustworthi-

ness. This section begins by attending to three of these—respect for persons, beneficence, and fairness—versions of which appear in the *Belmont Report* and in *Ethical Principles in the Allocation of Human Organs,* as well as in many other sources.[5] Then it considers scientific validity, which can be viewed as a subset of beneficence (utility) but which can be defended as an independent principle. The section closes with attention to trustworthiness in the form of an ethically trustworthy system of organ donation, transplantation, and research that can elicit and sustain public trust and thus promote organ donation and participation in research.

Respect for Persons

Respect for persons is a central and complex principle both in organ donation and transplantation and in research involving human participants. It includes, but is not reducible to, respect for personal autonomy, which is shorthand for respect for persons' autonomous choices. This principle, as this report interprets it, has several features and implications[6]:

- Respect for the dignity, worth, and value of each human being. In line with Immanuel Kant's ethics, this includes the right, among

[5]In its report, *Moral Science: Protecting Participants in Human Subjects Research*, the Presidential Commission for the Study of Bioethical Issues (2011b), established under President Barack Obama, noted that the rules in the Common Rule (and in the similar version for the U.S. Food and Drug Administration) reflect widely accepted principles of ethics. These principles are rooted in longstanding values that find expression in many sources of moral philosophy; theological traditions; and codes, regulations, and rules. They are the bulwark of ethically sound science, or "moral science," as the Commission terms it. Each generation may re-examine how these principles are contextually applied and understood. And, their application or implementation may vary depending on the level of risk that a subject faces. Medical research that poses risk of physical injury rightly raises more concerns than does routine social survey research, for example. Nonetheless, the same ethical principles govern all of these activities, and serve as enduring guideposts that must not be ignored (Presidential Commission for the Study of Bioethical Issues, 2011b, p. 3).

While the Presidential Commission at times refers to the Belmont principles, it also offers its own reformulation: "1. One ought to treat people fairly and with respect, 2. One ought not to subject people to harm or the risk of harm, even with their consent, unless the risk is reasonable and there is a proportionate humanitarian benefit to be obtained. 3. One ought not to treat people as mere means to the ends of others" (Presidential Commission for the Study of Bioethical Issues, 2011a, pp. 94–96). See also *Safeguarding Children* (Presidential Commission for the Study of Bioethical Issues, 2013), Chapter 2, which features the Belmont principles supplemented by a fourth principle of democratic deliberation which the Presidential Commission views as implicit in the National Commission's work. For further discussion of the Belmont principles and possible revisions and expansions, see Childress et al., 2005.

[6]Several of these specifications of respect for persons for deceased organ donation were articulated in *Organ Donation: Opportunities for Action* (IOM, 2006). The committee for the current report drew some formulations, with modifications, from that report.

other rights, to be treated not merely as a means, as an instrument, to others' ends (Kant, 1993).

- Respect for each individual's choices and preferences with regard to health care decisions and research participation. In the case of the latter, research participants bear risk in the context of research protocols that are primarily designed to advance medical knowledge. Participants are respected by a robust process of informed consent before they are enrolled in studies. When potential participants lack capacity,[7] respect for persons generally entails not exposing an individual to research procedures that exceed minimal risk—except where those risks are exceeded by the direct benefits to that individual. Surrogates' decisions about a currently non-autonomous person's participation in research should track that person's prior wishes, if known, or his or her values, when identifiable, as well as his or her overall best interests.
- Avoidance of undue pressure and coercion on a person's decisions, including decisions about whether to accept medical care, enroll in research, or donate organs.
- Respect for each competent person's right to decide whether to donate his or her organs and other biological materials after death for transplantation, research, education, etc. The individual's exercise of what is sometimes called "precedent autonomy" occurs within the UAGA, which provides the legal framework for the donation of biological materials. (Chapter 3 will spell out the way in which this right is embodied in the UAGA.)
- Recognizing the priority of a decedent's previously stated preferences, while being sensitive to the feelings and wishes of his or her family.
- Appropriate reliance on family and other surrogate decision makers when the decedent did not formally indicate his or her wishes through a registry, donor card, or other means. In general, surrogate decision makers, chosen by the decedent or authorized by law, should make their decisions in accord with the deceased person's preferences when known or, when those preferences are unknown, in accord with the person's values, when identifiable.
- Respect for a person's bodily remains following death.
- Avoidance of disrespectful practices and language. Once common terms such as "harvesting organs" or "cadaveric donors"

[7] The *Belmont Report* specifies the principle of respect for persons in two rules: (1) "individuals should be treated as autonomous agents," and (2) "persons with diminished autonomy are entitled to protection" (U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979).

have become problematic because they are now considered to be disrespectful toward donors and their families or surrogates (see Chapter 1 and IOM, 2006). Another arguably disrespectful phrase is "to consent a person" or "consenting a person." Indeed, in medical practice and in research, it has become common to hear someone say "I consented him" with reference to having sought and received an individual's consent for a procedure or for research participation. It is easy to understand why "consenting" a patient or research subject has become a convenient shorthand expression. However, professionals do not and, indeed, cannot "consent" others. And, from the standpoint of respect for persons, only individuals, their families, or other surrogates can consent to participation in research. Professionals provide the opportunity, information, and the like for consent, but consent remains the individual's or surrogate's prerogative, just as organ donation is the individual's or surrogate's prerogative.

- Respect for personal privacy and confidentiality.

Beneficence

The principle of beneficence includes duties not to harm others, to prevent harm to and remove harm from others, and to provide positive benefits. Some ethical frameworks distinguish a principle of beneficence from a principle of non-maleficence (Beauchamp and Childress, 2013), but the *Belmont Report*, instead, explicates the principle of beneficence through two complementary rules: (1) do not harm, and (2) maximize possible benefits and minimize possible harms (U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). The second rule points to the necessity and importance of balancing prospective benefits against possible harms (risks), costs, etc., in evaluating research involving human subjects. This version of beneficence is often identified as the principle of utility, for instance, in setting criteria for the allocation of donated organs, as in the OPTN Ethics Committee's report *Ethical Principles in the Allocation of Human Organs* (OPTN, 2015).

Beneficence or utility requires consideration of the ratios of probable benefits versus risks, costs, etc., in analyzing and assessing different policies, practices, and actions, all with the aim of producing a net balance of good. Sometimes this principle is implemented through formal analytical methods such as risk–benefit analysis or cost–benefit analysis. Other times it is implemented in less formal ways. In most frameworks, beneficence or utility is only one principle among several, and it is not always triumphant. It too must be balanced against other principles such as fairness or equity (U.S.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979; OPTN, 2015).

Criteria for organ allocation incorporate consideration of the probable success of the transplantable organs for potential recipients on the waiting list. After all, the aim is to benefit patients who need an organ transplant because they are critically ill. Success can be defined in various ways, such as graft survival, length of patient survival, or quality of life post-transplant, the latter two of which are sometimes expressed in quality-adjusted life years. The probability of success may hinge on a variety of factors related to a patient's condition, blood type, size of the organ, tissue match, etc. However the potential benefits are defined, they need to be balanced against the risks, in light of the patient's overall condition, the quality of the available organ, and the like. What might be called medical utility—as distinguished from social utility, that is, the maximization of social welfare—is thus important, but it is not the only ethical consideration in play. For some organs the waiting time for a transplant may be important, while for others the urgency of medical need may be crucial. The assignment of points for different factors builds in and features, but is not limited to, medical utility; it also includes other principles such as fairness.

Research involving human participants must pass a risk–benefit analysis and assessment in which the probable and possible harms to participants are evaluated against the probable benefits to future patients (as well as to research subjects if the research offers the possibility of benefit to them). It is important not only to minimize harmful effects (e.g., damage to organs) but also to evaluate risks in relation to the potential benefits for future organ transplant recipients. The evaluative process is even more complicated for the recipients of non-target organs, since organ donor intervention research, by design, does not directly seek to benefit such recipients, and yet they may face some risks. Careful attention should be paid to identifying when recipients of non-target organs need to receive human research subject protections (see the discussion in Chapter 3). Possible effects on the overall allocation of organs also merit attention. In addition to beneficence/utility, considerations of fairness must be brought into the distribution of benefits and risks and into the allocation of research organs. Subsequent chapters will further discuss these issues and propose a mechanism for monitoring these possible effects in terms of beneficence/utility and fairness.

Fairness

Determining what is due to individuals or groups involves a cluster of principles, including fairness, equity, impartiality, and justice. In making such determinations, it is common to distinguish the formal criterion of justice from material criteria of justice. The formal criterion dictates that

similar cases should be treated similarly and dissimilar cases should be treated dissimilarly (Beauchamp and Childress, 2013). Similarly situated persons are all entitled to treatment according to the same standards and through the same procedures and processes.

By contrast, material criteria of justice identify the relevant similarities and dissimilarities among individuals and groups and thus determine how specific benefits and risks, costs, and burdens should be distributed (Childress, 2001). For example, debates about allocating scarce medical resources have focused on which material criteria are morally relevant, such as urgency of need, probability of success, societal contribution, or ability to pay. Agreement can usually be reached that certain criteria, such as race or gender, are unacceptable because they are based on morally irrelevant characteristics to that specific discussion, but securing agreement on the morally relevant characteristics for allocation is more difficult (Childress, 2001).

At least since the publication of the 1986 report of the U.S. Task Force on Organ Transplantation, donated organs have been viewed as a scarce national resource (U.S. Task Force on Organ Transplantation, 1987). Organ procurement and transplant teams act as trustees of donated organs on the behalf of the public. Their authority over the distribution process is not absolute, but rather falls within acceptable material criteria for distribution (Childress, 2001). In general terms, the criteria for organ allocation focus on medical need, the probability of successful outcomes (medical utility), and time spent waiting by the potential recipients. Depending in part on the organ under consideration, there are debates about how much weight should be given to each of these factors (Ubel and Loewenstein, 1996; Neuberger et al., 1998; Tong et al., 2010). Allocation algorithms are devised to operationalize weighted criteria, and they are updated as science advances, technologies improve, evidence emerges about disparities and inequities, and other critical changes.

Considerations of fairness also shape *who* should be involved in formulating the material criteria for organ allocation. Participatory justice requires the involvement of affected stakeholders in setting distributive criteria. The idea that donated organs belong to the community implies that public participation is crucial in the deliberative processes for determining allocation criteria (U.S. Task Force on Organ Transplantation, 1987). UNOS has followed through accordingly: its organ allocation policies are developed in public, with public input, and subjected to public scrutiny (OPTN, 2017). This is vitally important for public trust. Although the phrase "transplant community" has sometimes been limited to including just transplant professionals, transplant recipients, and donor families, it is possible to adopt a broader interpretation that includes the public at large because all members of society are potential organ donors and potential

family members of organ donors as well as potential transplant recipients and members of their families.

Several fairness concerns arise in the context of organ donor intervention research. As in all research, the current recipients of research organs bear some risks for future organ transplant recipients. Hence, there should be a fair distribution of probable benefits and risks between present and future generations. Another question of fairness concerns current candidates on the waiting list who are either unwilling to accept an organ involved in research or not eligible for a specific research protocol and thus may experience a longer wait for a transplant, thereby incurring an increased risk of serious and extended morbidity or even death before they receive a transplant. This situation raises not only questions of fairness in organ allocation but also questions about whether the situation creates undue pressure that infringes on the principle of respect for persons.

Other questions of fairness surface in considering the impact of organ donor intervention research on non-target organs—that is, organs that may be affected by the research intervention even though they were not the intervention's intended target. For example, even if a particular research intervention targeting a deceased donor's kidneys will probably not have a negative impact on the efficacy or safety of a heart transplanted from the same donor, it may not be possible to completely rule this out. While the research is not designed to benefit the recipients of non-target organs, now or in the future, the fact that these recipients bear some risks, as noted earlier, provides a rationale based on fairness for viewing them as potential research participants with the institutional review board making decisions regarding informed consent.

There is uncertainty surrounding some of these possible effects, at least for now. Thus, systematic oversight and monitoring, examined in Chapter 4, will be required to determine whether the potential negative effects actually occur for candidates on the waiting list for a particular target organ or for recipients of non-target organs; if they do, OPTN/UNOS, along with other appropriate organizations, will need to determine the best course of action to ensure the fair distribution of benefits and risks. Nevertheless, it may be possible to anticipate and address some issues of fair distribution in advance. For example, oversight should include attention to divergent views among transplant teams about whether they, acting on behalf of their patients, would be willing to accept target or non-target organs subjected to a particular type of intervention.

Validity

Validity refers to the approximate truth of inferences derived from measurements or research, or both (Shadish et al., 2015). Many research

activities are designed to generate evidence to support scientific and clinical decision making. For any research activity to fulfill that purpose, its output must provide a truthful representation of underlying causal processes and relationships. Thus, the requirement of validity dictates that for any research involving human subjects to be ethical, it must produce evidence that is sufficiently reliable to guide decision making in research and clinical care.

In many bioethical discussions, the concept of validity is implied by beneficence or utility because only valid research can produce benefits. For example, the *Belmont Report* states that research should "maximize possible benefits," including benefits to society in the form of generalizable knowledge (U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). Whereas beneficence or utility can find expression in many ways (e.g., enhancing patient welfare or maximizing the number of individuals who benefit from knowledge), validity signals that research activities should be pursued in such a manner that the resulting findings provide a truthful representation of biological reality, including the merits of a particular treatment strategy. As a principle, validity identifies a condition toward which researchers should strive. It has significant implications even when the research is risk neutral or minimally risky and thus easily passes a risk/prospective benefit analysis. The principle of validity moves beyond risks to research subjects as balanced against benefits to them and to the society to include the risks to society of failing to produce valid research. It indicates that downstream users of knowledge have a claim on the reliability and comprehensiveness of the information generated from the research activity.

Whether viewed as a separate principle or as a requirement of beneficence/utility, validity indicates the need to design studies in a way that supports valid clinical inferences. For example, when comparing two treatments, the use of blinded treatment allocation minimizes the impact of observer bias on measurements; delivering treatments in studies in a manner that is consistent with the intended clinical scenarios is another way of maximizing the validity of clinical inferences in trials. The principle of validity also requires that studies be reported in ways that enable independent experts to make valid inferences. For example, detailing patient characteristics and flow through a trial, clearly describing methodologies, and reporting all outcomes and analyses will help independent experts formulate an accurate understanding of a study's findings.

Growing evidence indicates that avoidable threats to validity are common in medical research. For example, a sizeable fraction of completed trials is never published, with studies that failed to meet their primary endpoint with statistical significance being published less frequently than studies that succeeded (Dickersin, 1990; Hakala et al., 2015). Many clinical trials—including those published in high-impact venues—alter their

primary endpoints (Mathieu et al., 2009; Vedula et al., 2009) or deviate from protocols (Chan et al., 2004) when publishing results. Such selective outcome reporting can lead to bias. Still another threat to validity stems from underpowered studies that lack adequate statistical power to answer their research questions (Halpern et al., 2002).

When conducting research, researchers must contend with numerous factors in experimental systems that interfere with accurate and precise estimates of treatment effects, including random variation, measurement error, and confounders. In addition, various social factors—such as unconscious bias, financial interest, or professional incentives that reward only "positive" findings—can impede proper scientific conduct. In the context of organ donor intervention research, the principle of validity stipulates that, when conducting donor intervention studies, researchers and oversight structures should minimize any factors that introduce validity threats, while encouraging those practices—including transparency, reporting, and rigorous study design—that facilitate an accurate understanding of the treatment effect for a donor intervention.

Trustworthiness

Trust is vitally important in organ donation and transplantation. Indeed, according to Kenneth Moritsugu, a member of the National Academies of Sciences, Engineering, and Medicine committee and a physician, who was involved in the donation of the organs of his deceased wife and, on another occasion, the organs of his deceased daughter, trust is "the heart" of organ donation and transplantation. He identified several types of trust:

- Trust that the health care team will do all it can to care for an individual who is very sick or injured.
- Trust that chaplains will bring comfort and solace when nothing more can be done to save a loved one.
- Trust that the designated requester from the organ procurement organization is accurately representing the decision that the deceased individual made to be an organ and tissue donor when he or she was of sound mind and body.
- Trust that the surgical team will recover those organs and tissues to the maximum extent medically possible and that they will treat the deceased individual with dignity and respect.
- Trust that the transplant team will carefully place the recovered organs and tissues to ensure that the grafts will be successful and benefit the recipient, that they will use the organs for the purpose for which they were donated, and that they will treat them, as well as the donor and the recipient, with dignity and respect.

- Trust that the post-transplant team will do what is necessary to nurture the newly transplanted recipient back to health.
- Trust that transplant recipient will be a careful caretaker of this gift of life.
- Trust that the recipient's family and friends will continue to assist their loved one to return to a full life and that the recipient and family and friends alike will realize the great gift they have received.
- Trust that the community and society will fully appreciate the benefits of organ and tissue donation and transplantation.

Trust can be defined as confidence in others to act in certain ways. Confidence in others to act ethically presupposes their capacity to do so based on their knowledge, technical competence, and expertise, which together will enable them to handle complex situations such as organ donation, transplantation, and research. Such trust is important—but also fragile—throughout health care (Shore, 2006), but it is particularly important in organ donation/transplantation and in research involving human subjects. Neither organ transplantation nor human subjects research can proceed without the public's trust. Absent such trust, individuals and families would not be willing to donate organs or to participate in research designed to generate generalizable knowledge.

Rather than attempting to manufacture public trust so that these important activities can proceed, the goal should be to design and implement trustworthy systems of organ donation, transplantation, and research that can appropriately sustain trust over time. A trustworthy system can serve as the basis for public trust that is warranted. Such a system attends to and embodies the other ethical principles examined in this chapter. Not only are these principles important in and of themselves, but a strong consequentialist reason also supports adherence to them: organ donation and transplantation and research with human subjects cannot succeed without demonstrated adherence to those principles as a basis for public trust.

Clearly a lack of trust or frank distrust can hamper organ donation and transplantation. In public opinion surveys, respondents give several reasons for not registering as organ donors, such as not having thought about organ donation or not wanting to contemplate death (IOM, 2006; HRSA, 2013). In addition, respondents sometimes indicate, directly or indirectly, that they do not trust the organ donation and transplantation process. Specifically, some worry that registration as an organ donor carries risks. For instance, a 2010 survey by Donate Life Northwest reported that

- 52 percent of respondents believe that doctors may not try as hard to save their lives if the doctors know that they are registered as organ or tissue donors.

- 48 percent of respondents believe a black market exists in the United States for organs and tissue, up from 44 percent in 2009.
- 61 percent believe that brain dead persons can recover from their injuries (Donate Life Northwest, 2010).

The large percentage of respondents with beliefs about donation and transplantation that are inaccurate highlights the challenges that the donation and transplantation communities face and the hurdles that need to be overcome (IOM, 2006). Even when opinion surveys do not specifically ask about distrust or mistrust, reported beliefs such as these reflect limited trust.

A perception that organ allocation systems are unfair—for instance, a perception that some individuals receive preferential access to organs—can also dissuade people from donating their own or a relative's organs. The public needs to be able to trust that the criteria for organ allocation are fair and that they are applied impartially. A 2012 national survey found that approximately 65 percent of the U.S. population agreed somewhat or strongly that the transplant system uses a fair approach to deceased organ distribution, with just over 20 percent strongly agreeing (HRSA, 2013). In this survey, confidence in the fairness of organ distribution aligned with an expressed willingness to donate among different age cohorts. This suggests that any direct or indirect impact on organ allocation from organ donor intervention research must be carefully evaluated in light of both the standards and the perceptions of fairness in organ distribution. Otherwise public trust may suffer.

Racial and ethnic minorities tend to have lower rates of organ donation (Goldberg et al., 2013) and to be less willing to participate in research (Cobb et al., 2014). Social and economic marginalization, as well as distrust in medical research that has its roots in historical abuses, have likely made members of minority groups less likely to participate willingly in organ donation and research (Shavers et al., 2000; Bratton et al., 2011). Mistrust among minorities has several targets, including the health care system with its lack of equity (Siminoff et al., 2006) and doctors, scientists, and the government (Corbie-Smith et al., 1999). There is reason to believe that such mistrust has been exacerbated by research scandals such as the notorious 40-year U.S. Public Health Service study of untreated syphilis in several hundred African American males in and around Tuskegee, Alabama. "The symbolic power of 'Tuskegee' works because of the revulsion" over the deception, lack of informed consent, and exploitation that marked this study (Reverby, 2009, p. 232).

Transparency is a crucial precondition for engendering and sustaining public trust. In the context of the current report, transparency requires enabling the public to understand clearly what is involved in organ donor intervention research in order to obviate possible suspicions that the re-

search might endanger the welfare or rights of organ donors or of transplant candidates and recipients. For this research to proceed and succeed, trust is needed on the part of prospective individual or surrogate donors of organs as well as on the part of prospective recipients who may become research subjects by accepting organs involved in research. Transparency needs to be accompanied by public education in a variety of forms and venues. Another potentially valuable step is engaging the public in developing standards and procedures. In line with UNOS's efforts to obtain public input in setting the criteria and point systems for fairly allocating donated organs, public engagement has also been recommended for other policies regarding organ donation and transplantation (Sher, 2008). Beyond transparency and public engagement, strong oversight is also potentially important in creating and maintaining a trustworthy system. In Chapter 4 the committee proposes a three-part structure for the robust oversight of organ donor intervention research.

Finally, not only is trustworthiness a necessary precondition for organ donor intervention research to thrive—through authorization for organ donation and consent to participate in research—but the research itself must not compromise the trustworthiness of the system of organ donation and transplantation or damage public trust.

CONCLUSION

This chapter has described several ethical principles that can structure deliberations, guide policy, and inform decisions about organ donor intervention research. These principles become particularly important in settings where legal and regulatory frameworks set minimum standards but are indeterminate in their applications or incomplete in their incorporation of ethical concerns. They are also important in cases where these legal and regulatory frameworks appear to need reassessment because they create unwarranted obstacles to progress in increasing the quantity and improving the quality of transplantable organs. Even though there is a rough consensus about the value of these broad principles, variations in interpretations of their meaning and implications arise, particularly as applied to such projects as organ donor intervention research. Moreover, within the consensus that these broad ethical principles are valuable, disagreements may also emerge about exactly how to balance these principles if they come into conflict in assessments of policies and practices.

The existence of possible differences in understanding the content and the weight of ethical principles in particular situations indicates that the committee's task requires much more than the simple application of ethical principles. Instead, its task is inevitably one of interpretation as it considers different possible ways to undertake organ donor intervention research in

light of these principles and in light of the pertinent legal, regulatory, and policy frameworks as well as current institutional, organizational, and professional responsibilities, opportunities, and constraints. Throughout the report the committee has highlighted various aspects of this research that need further attention and modification to make it worthy of the public's trust.

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3

Legal, Regulatory, and Policy Frameworks for Organ Donation and Research Participation

Despite the increase in the rate of organ donations from deceased donors in recent years, the demand for deceased donor organs continues to exceed the supply of transplantable organs (see Chapter 1), making it important to maximize transplant opportunities and the likelihood that available organs will adequately function in recipients. Organ donor intervention research has the potential to improve outcomes for transplant recipients and to increase the number of transplants. Nevertheless, realizing this potential depends on the willingness of donors and their surrogates to allow the research to be done and on the willingness of transplant teams and transplant candidates to accept organs on which research has been performed. Trust in the U.S. organ donation and transplantation system and its processes involves confidence in and reliance on facts and nuances being fully and fairly communicated. Questions remain as to what the donation and transplantation community and society as a whole *should* do to maintain that trust, as opposed to what merely *must* be done to be in legal and regulatory compliance.

Obtaining authorization for donation from organ donors (or their surrogates) and consent for transplantation from transplant candidates has been required for decades. However, the conduct of organ donor intervention research raises important questions regarding the authorization and consent processes for both donors and transplant candidates:

1. From an ethical and policy perspective, is authorization from the donor or the donor surrogate required to conduct research on

donated organs prior to transplantation? If yes, to what level of detail?

2. Does a donor's authorization for transplantation automatically include authorization for research followed by transplantation? If so, under what circumstances?
3. From an ethical and policy perspective, is consent from the potential organ recipient needed prior to that individual accepting a donated organ that has been involved in research? If yes, to what level of detail? How should these research processes be structured and organized to ensure a trustworthy system (see Chapter 4)?

DECEASED ORGAN DONOR INTERVENTION RESEARCH STUDIES: EXAMPLES

In setting the context for its examination of this research, the committee reviewed 15 clinical studies that involved organ donor intervention research in order to determine (1) how researchers in the United States interpret the laws and regulations that apply to their studies, and (2) how studies conducted in countries other than the United States, which are subject to different laws and regulations, address these questions (see Table 3-1). This is only a snapshot of organ donor intervention studies (reviews include Feng, 2010; Dikdan et al., 2012) and points to issues to be discussed throughout the chapter regarding research authorization from donors and donor families and consent from transplant recipients.

Examples of Organ Donor Intervention Research Studies: Authorization for Research on Deceased Organ Donors

The investigators in several of the studies listed in Table 3-1 obtained authorization prior to including deceased donors in their research protocols. In studies by Ware and colleagues (2014) and Niemann and colleagues (2015), for example, if a deceased donor had not previously authorized donation, then the investigators asked the potential donor's surrogate to authorize donation for the purposes of transplantation and of research. Niemann and colleagues (2015) noted that in the cases where a surrogate declined donation for the purpose of research out of concern that the organ would be used solely for research, the surrogate was asked whether donation would be authorized specifically for the study in question since the study included research followed by transplantation; in cases where a surrogate then agreed to research, "an addendum was made to the authorization form specifically stating authorization for enrollment in this donor management trial" (Niemann et al., 2015, supplementary appendix, p. 7).

In their review of authorization procedures used in a range of studies conducting deceased donor intervention research, Rey and colleagues (2011) noted:

> If the decedent's preferences are known, corresponding consent standards for organ donation should be followed; family assent would be encouraged but not required for decedents who had indicated preferences for research participation, and surrogates would not be authorized to consent if the decedent had clearly refused. (p. 281)

The committee's analysis of the laws, regulations, and procedures for obtaining authorization for deceased organ donors will be provided later in this chapter.

Examples of Organ Donor Intervention Research Studies: Research Consent from Recipients of the Target Organ

Whether the research protections for human subjects that are detailed in the U.S. Federal Policy for the Protection of Human Subjects, the Common Rule, apply to recipients of organs that have been part of a research study has been the subject of debate and concern (Rey et al., 2011; Glazier et al., 2015; Carome and Wolfe, 2016). The majority of the studies summarized in Table 3-1 did not obtain research consent from the recipients of the organ that was the target of a deceased donor intervention. In those studies that did not obtain consent, the rationale was not fully detailed in the published description of the study. Ware and colleagues (2011) explained that

> informed consent from lung recipients is not required in the BOLD study because the study poses minimal risk, it has traditionally been the role of the transplant surgeon to determine the relative risk of an organ, and, finally, there is no precedent in the transplant community for requiring recipient consent for donor management studies that pose minimal risk. (p. 54)

By contrast, Rey and colleagues (2011) offered the opinion that "recipients may obtain organs subjected to the donor interventions or organs from a control donor" and they are thus "no less 'human research subjects' than are recipients of blood products, bioprosthetic devices, or pharmaceuticals that have been randomly assigned to one or another preparative intervention" (p. 281).

One of the studies involved research interventions and data collection on the donors only, with no data collected from the recipients (i.e., Pérez-Blanco et al., 2005). (Note this study was not conducted in the United States and would have been subject to different laws and regulations.) Rey

TABLE 3-1
Case Studies Involving Organ Donor Intervention Research

Study Authors	Study Publication Year	Location	Donor Intervention	Target Organ	Non-Target Organ(s) Followed
Studies Conducted in the United States					
Niemann et al.	2015	CA and NV, U.S.	Hypothermia	Kidney	All
Ware et al.	2014	CA and NV, U.S.	Nebulized Albuterol	Lung	All
Guarrera et al.	2010	NY, U.S.	HMP	Liver	n/a[a]
Koneru et al.	2005	NJ, U.S.	IPC	Liver	None
Studies Conducted Outside of the United States					
Bral et al.	2017	Canada	NMP	Liver	n/a[a]
Ravikumar et al.	2016	U.K.	NMP	Liver	n/a[a]
Oniscu et al.	2014	U.K.	NRP	Kidney, Liver, Pancreas, Lung	None
D'Amico et al.	2013	Italy	NAC	Liver	None
Watson et al.	2010	U.K.	HMP v CS	Kidney	n/a[a]
Jochmans et al.	2010	Europe	HMP v CS	Kidney	n/a[a]
Schnuelle et al.	2009	Europe	Dopamine	Kidney	All
Moers et al.	2009	Europe	HMP v CS	Kidney	n/a[a]
Venkateswaran et al.	2008	U.K.	MP +/– T3	Lung	Heart, Liver, Kidney
Kotsch et al.	2008	Germany	MP	Liver	Kidneys
Pérez-Blanco et al.	2005	Spain	T3	Liver, Pancreas, Heart, Lung	None

NOTE: CS = cold storage; HMP = hypothermic machine perfusion; IPC = ischemic preconditioning; IRB = institutional review board; MP = methylprednisolone; n/a = not available; NAC = N-Acetylcysteine; NMP = normothermic machine perfusion; NRP = normothermic regional perfusion; OPO = organ procurement organization; RCT = randomized controlled trial; T3 = triiodothyronine; U.K. = United Kingdom.

[a]Ex vivo research, no non-target organ(s).

[b]Consent for participation in research was not explicitly stated in article.

	RCT	# of OPOs/ Centers	# of Donors	# of Recipients	Reviewed by IRB	Consent from Donor or Surrogate for Research	Consent from Recipient of Target Organ	Consent from Recipient of Non-Target Organ
	Yes	2	370	572	Yes	Yes	No	No
	Yes	1	506	152	Yes	Yes	No	No
	No	1	40	40	Yes	Unknown	Yes	n/a[a]
	Yes	1	62	62	Yes	No	Yes	No
	No	1	10	9	Yes	Unknown	Yes	n/a[a]
	No	2	20	20	Yes	Yes	Yes	n/a[a]
	No	3	21	49	No	No	No	No
	Yes	1	214	140	Yes	No	Yes	No
	Yes	5	46	90	Yes	No	Yes	n/a[a]
	Yes		206	164	Yes	No	No	n/a[a]
	Yes	60	264	487	Yes	Yes	No	No
	Yes	60	336	672	Yes	Yes[b]	No	n/a[a]
	Yes		60	48	Yes	Yes	No	No
	Yes	1	100	100	Yes	Yes[b]	No	No
	Yes	1	52	None followed	Yes	Yes	No	No

SOURCES: Koneru et al., 2005; Pérez-Blanco et al., 2005; Kotsch et al., 2008; Venkateswaran et al., 2008; Moers et al., 2009; Schnuelle et al., 2009; Guarrera et al., 2010; Jochmans et al., 2010; Watson et al., 2010; D'Amico et al., 2013; Oniscu et al., 2014; Ware et al., 2014; Niemann et al., 2015; Ravikumar et al., 2016; Bral et al., 2017.

and colleagues (2011) argued that, strictly speaking, in the types of studies where no data are collected from recipients, the recipients might not be considered human research subjects under current regulations.

> For example, if outcomes of such studies were limited to metrics such as the number of organs recovered or results of recovered organ biopsies [performed before transplantation], then recipients would not be research participants because there are no recipient data collected. Recipient consent would be unnecessary. (Rey et al., 2011, p. 282)

But these same authors go on to argue that there is little difference, from the perspective of the recipient, between donor intervention studies that collect data on the recipients and those that do not; "in both cases, recipients are exposed to similar risks and could receive similar organs. Thus, requirements for research consent should apply equally to all recipients of organs regardless of investigators' decisions to collect recipient data" (Rey et al., 2011, p. 282).

Disclosing clinical risks is a routine part of the process for obtaining consent from a candidate for organ transplantation. In the above interpretations of regulations, disclosing clinical risks is viewed as including the disclosure of clinical risks that arise from research involved organs. This issue will be explored below, along with the debate about whether in the absence of collecting specific, additional data for research purposes—that is, beyond the clinical data routinely reported about transplant recipients—recipients of research organs are research subjects whose research-related consent is also required.

Examples of Organ Donor Intervention Research Studies: Research Consent from Recipients of Non-Target Organs

When a research intervention is administered to a deceased donor prior to organ recovery and the intent is to have an effect on a specific organ such as a kidney (i.e., the target organ), the intervention could potentially affect other organs that will also be transplanted (i.e., non-target organs). None of the studies included in Table 3-1 indicated that they had sought consent from the recipients of non-target organs. However, the reasons that argue in favor of considering the recipients of target organs as human research subjects may apply equally to recipients of non-target organs because the research intervention may have an impact on the non-target organ and thus on its recipient. The potential for effects on non-target organs was explicitly recognized by Niemann and colleagues (2015 [noted in supplementary materials to the journal article]), and they excluded deceased donors who had the potential to donate a heart or a lung from the trial until preliminary

data provided assurance that hypothermia did not have deleterious effects on these organs. Notably, the preliminary data did not rule out the possibility of deleterious effects but instead provided evidence that any such effects were not dramatic enough to become apparent in the preliminary data. Similarly, donors with the potential for split liver donation were permanently excluded from the trial because of the potential for hypothermia to have deleterious effects on coagulation during dissection. These concerns about non-target organs highlight the possibility that some interventions, such as adjusting the body temperature of a donor, could influence any organs subsequently transplanted from that donor. This report will examine the controversies surrounding whether and under what conditions recipients of non-target organs become research subjects and need to be so informed so that they can choose whether to provide research-related consent or refusal.

OVERVIEW OF THE LAWS AND REGULATIONS GOVERNING ORGAN DONATION, TRANSPLANTATION, AND RESEARCH PARTICIPATION

Uniform Anatomical Gift Acts

The United States operates its organ donation system under an "opt-in" model in which the individual while alive or the next of kin or surrogate after the individual's death must explicitly choose to donate organs. In contrast, several European (e.g., Austria, Belgium, France, and Spain) and South American (e.g., Argentina, Colombia) nations utilize an "opt-out" system that presumes donor authorization and participation in the absence of an explicit objection (Shepherd et al., 2014; Samuel, 2017). U.S. states began enacting organ donation and procurement legislation in the 1960s when organ transplantation became a viable medical procedure. In 1968 the National Conference of Commissioners on Uniform State Laws promulgated the Uniform Anatomical Gift Act (UAGA) with the intent of promoting uniformity among states and simplifying the process of obtaining organs from deceased persons (Goodwin, 2006). The UAGA is not a federal law, but rather is a template that states can use in developing their own laws governing anatomical gifts. Each state and the District of Columbia adopted the 1968 UAGA (AOPO, 2017). Due to its universal adoption, the 1968 UAGA is sometimes mistaken as federal law.

The act permitted adults of sound mind to donate all or any body parts at death and required that donor intent be expressed in writing and signed by the declarant and two witnesses. In the absence of the decedent's authorization of donation prior to his or her death and in the absence of the decedent's known objection, the UAGA permitted the decedent's next of kin to donate the decedent's organs. To minimize confusion regarding

who among next of kin is legally authorized to donate, the UAGA ranks relatives' legal authority to donate their deceased kin's organs by status. For example, the law ranks spouses above siblings, adult children, and parents. Even though the 1968 UAGA assigned priority to the decedent's prior decision to donate, it did not clearly state that the decedent's decision to donate (in contrast to the decedent's objection to donation) should override the next of kin's choice (NCCUSL, 1968). However, this priority was explicitly stated in the Comments to the 1968 UAGA: "Subsection (e) [of Section 2] recognizes and gives legal effect to the right of the individual to dispose of his own body without subsequent veto by others" (NCCUSL, 2003, p. 117). The lack of clarity in the UAGA itself (in contrast to the Comments), made it easier for organ procurement teams to allow objecting next of kin to override the decedent's prior expressed decision to donate organs (Goodwin, 2006).

The commissioners revised the UAGA in 1987 and again in 2006. The revisions in the 1987 UAGA were intended to accomplish several goals. First, they were intended to increase the supply of organs to meet rapidly growing demand. That is, while the 1968 UAGA clarified the status of who was legally authorized to donate, it did not explicitly attempt to increase the organ supply (NCCUSL, 1987), even though that was an implicit goal. Second, the 1987 UAGA was drafted to come into compliance with the newly adopted federal law, the National Organ Transplant Act (NOTA).[1] NOTA, enacted in 1984, banned the exchange of organs for "valuable consideration," for example, paying donors for organs (NCCUSL, 1987). The 1968 UAGA had not indicated whether organs could be sold, leaving the issue open to interpretation (NCCUSL, 1968). The 1987 version adopted the ban on selling organs, but the "valuable consideration" language of NOTA was (and continues to be) subject to interpretation by the U.S. Department of Justice. (A more detailed discussion of NOTA appears in the following section.)

The 1987 UAGA also removed the requirement that two witnesses sign the donation document. Furthermore, it stressed that an individual's choice to donate organs cannot be revoked by others, thereby removing any uncertainty in this matter. It also granted medical examiners and coroners the authority to authorize the removal of a "body part" for transplantation under certain conditions when no prior objection by the decedent was known (sometimes misleadingly termed "presumed consent") and when efforts had been made to contact the next of kin (NCCUSL, 1987). Only 26 states adopted the 1987 UAGA—other states adopted non-uniform amendments to their anatomical gift acts—resulting in a lack of uniformity among the states (NCCUSL, 2006).

[1] National Organ Transplant Act, Public Law 98-507, 98th Cong. (October 19, 1984).

Drafters of the 2006 UAGA removed the provision that allowed medical examiners and coroners to authorize removal of a "body part" for transplantation (NCCUSL, 2006), particularly in response to controversies that had arisen regarding body part removal without authorization and to disparities in race and class that had been observed in these decisions. For example, a California study revealed that more than 80 percent of "presumed consent" cornea donors were black and Latino and that none of the families had been notified that the Los Angeles Coroner's office had procured their decedents' corneas (Goodwin, 2006). In some instances, where corneas were recovered, the relatives were not asked about their authorization for donation (Frammolino, 1997a,b) and others explicitly stated that they did not authorize donation (Goodwin, 2006). Some municipalities were sued in the wake of the 1987 UAGA, specifically in relation to this provision (O'Neill, 1998). Relatives of persons whose tissues were removed without authorization claimed that the states had violated their constitutional rights and desecrated their deceased relatives' bodies.[2]

Like the prior iterations of the UAGA, the 2006 law—the most recent version (last amended in 2009)—provides that individuals aged 18 years or older may choose or refuse to make an anatomical gift. The law also permits anyone applying for a driver's license to offer authorization, allows for symbolic or oral communication of donative intent, disallows the possibility of authorization for the removal of body parts for transplantation by a medical examiner's office without the decedent's or the surrogate's authorization, and lets individuals other than the decedent make an anatomical gift unless the decedent expressly refused donation during his or her lifetime. The gift may be of the entire body or parts of the body, and the donor determines whether the gift will be used for education, teaching, research, or transplantation. The UAGA establishes the donation as property that can be transmitted to others by authorization of the decedent before death, by will, by next of kin or surrogate after death, or, in their absence, by the state (NCCUSL, 2006). This statutory scheme is similar to that provided for other forms of property. With the goal of improving uniformity in the organ donation legislation across states, the 2006 UAGA, like the 1987 version, includes a first-person authorization provision preventing any family member or other responsible party from overriding a decedent's documented wish in favor of donation, just as they cannot override the decedent's refusal to make a gift. The act allows for express authorization to make an anatomical gift in several forms, including through a statement or symbol on a driver's license or a donor card or via a donor registry (NCCUSL, 2006).

[2] *Newman v. Sathyavaglswaran*, 287 F.3d 786, 800 (9th Cir. 2002); *Brotherton v. Cleveland*, 923 F. 2d 477, 481 (6th Cir. 1991).

As of June 2017, 46 states, the District of Columbia, and the U.S. Virgin Islands had adopted the 2006 UAGA (Uniform Law Commission, 2017b). However, many of the states that enacted the 2006 UAGA have added or modified amendments, while others have yet to adopt the updated act (Verheijde et al., 2007, HRSA, 2011). As a result, the application of the 2006 UAGA remains inconsistent (Uniform Law Commission, 2017a). Furthermore, each state maintains its own donor registry with many of these registries linked to drivers' licenses. States also may differ on what qualifies as authorization (HRSA, 2011). Despite these differences, all states must comply with the federally mandated ban in NOTA on the exchange of organs for "valuable consideration" because federal law supersedes any state provisions on this issue.

National Organ Transplant Act of 1984

No national system existed before 1984 to oversee the recovery and allocation of organs from deceased donors for transplant. Because organs were in short supply, there was competition for and unequal access to donor organs. In response, Congress passed NOTA (McDonald, 1988). The intent of NOTA is to ensure an equitable allocation of donor organs and to increase the number of organs available for transplantation. NOTA defines organs as the heart, lungs, liver, kidney, pancreas, and other organs, such as the small intestine, designated by the Secretary of the U.S. Department of Health and Human Services (HHS). NOTA also bans the sale of human organs for transplantation, with violations of the law punishable by up to 5 years in prison and a fine of $50,000. However, NOTA allows transplant surgeons, hospitals, transporters, and organ procurement organizations (OPOs) to receive compensation for their services. Following NOTA's enactment, the Uniform Law Commission amended the UAGA, as noted above, to prohibit the purchase and sale of organs for transplantation (NCCUSL, 1987), but generally it remains legal to purchase and sell blood products, sperm, and ova (Cohen, 2012).

NOTA authorized the Secretary of HHS to form the nationwide Organ Procurement and Transplantation Network (OPTN) to coordinate the donation and transplantation system and process. The Omnibus Budget Reconciliation Act of 1986[3] requires that all medical centers performing organ transplantation participate in the OPTN or forfeit their eligibility for federal Medicare and Medicaid payments. While membership in the OPTN is voluntary, in practice this legislation made membership in the OPTN and

[3] Omnibus Budget Reconciliation Act of 1986, Public Law 99-509, 99th Cong. (October 21, 1986).

compliance with OPTN policy mandatory for all U.S. transplant centers because all of them accept federal payments.

In 1998 HHS promulgated regulations known as the "Final Rule"[4] to guide both the structure and the operation of the OPTN and to direct the OPTN to standardize transplant waitlist criteria and to group transplant candidates by medical urgency in order to allocate organs to the sickest patients first. Per NOTA requirements, the OPTN maintains a national waitlist of organ transplant candidates, allocates deceased donor organs to candidates on the waitlist, establishes policies concerning organ allocation, sets quality standards for the acquisition and transplantation of organs, coordinates the transportation of organs from OPOs to transplant hospitals, analyzes and publishes data concerning transplantation, and reports comparative costs and outcomes from the nation's transplant centers.

The United Network for Organ Sharing (UNOS) is a private nonprofit entity under contract with the Health Resources & Services Administration (HRSA) to operate the OPTN. NOTA also established regional OPOs, which are nonprofit entities responsible for coordinating the acquisition, preservation, and transportation of organs from donor hospitals to transplant centers. OPTN divides the United States into 11 geographic regions, which are further divided into donation service areas (DSAs); a DSA is a defined geographical area that is served exclusively by a single OPO (OPTN, 2017a). The DSAs vary widely in terms of population size, the number of transplant centers and candidates, and the death rate of potential organ donors (SRTR, 2017b). UNOS promulgates the policies and standards for OPOs, and all OPOs are members of the OPTN (OPTN, 2017d). Members of the OPTN also include transplant centers, histocompatibility laboratories, medical scientific organizations, and public organizations.

The OPTN's policies primarily focus on how individual organs are allocated among waitlisted candidates. There are separate policies for each organ (heart, lungs, liver, kidneys, intestine, and pancreas). Allocation policies take into consideration the location of the transplant candidates and the first criterion for the matching process, with the exception of livers, is the identification of a candidate within the OPO or donor hospital's DSA. If a suitable candidate is not found locally, OPTN/UNOS can offer the organ to regional candidates, followed by national candidates (OPTN, 2017a). OPTN/UNOS uses allocation algorithms that consider compatibility and other factors to identify suitable transplant candidates for specific organs. In general, the algorithms take into consideration a candidate's current medical condition, the length of time spent waiting for an organ, and in some cases a candidate's prognosis as determined by objective clinical tests (OPTN, 2017a). The allocation systems frequently undergo revision.

[4] 42 C.F.R. Part 121.

The transplant coordinator from a transplant center enters each transplant candidate's medical information into the OPTN/UNOS database, UNet[SM], and designates the candidate as "active"—meaning that the candidate can receive an organ at any given time—or "inactive"—meaning either that the candidate is not medically suitable for transplantation at that time or that the candidate needs to complete eligibility requirements before being listed as active. The database matches information about a donor organ with the medical characteristics of active candidates on the waitlist. This generates a list that ranks active candidates according to the allocation rules. The OPTN offers the organ to the transplant center of the top-ranking matched candidate. If the organ is refused by either the transplant candidate or the candidate's transplant hospital, the OPTN contacts the next highest ranking matched candidate's transplant center. The process continues until the OPTN finds a candidate (and transplant hospital) willing to accept the organ (OPTN, 2017a). OPOs receive fees for coordinating this process; under NOTA these fees are defined as "reasonable payments associated with the removal, transportation, processing, preservation, quality control, and storage of a human organ."[5]

In 1987 NOTA established the Scientific Registry of Transplant Recipients (SRTR) to track information about transplant candidates and recipients and transplant procedures that are deemed necessary for the ongoing evaluation of organ transplantation. The SRTR databases contain both historical and up-to-date information about the transplantation process, including detailed information on waitlist candidates, transplant recipients, and survival statistics. These data help inform the development of "evidence-based policy to support analysis of transplant programs and OPOs, and to encourage research on issues of importance" related to transplantation (SRTR, 2017a).

The Common Rule

The Federal Policy for the Protection of Human Subjects, or the Common Rule, was published in 1991 and is the basic set of U.S. federal regulations that protect all human subjects in any federally funded research. Specifically, it states "the basic provisions for institutional review boards, informed consent, and Assurances of Compliance," and it "applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research."[6] In addition, "Research that is neither conducted nor supported by a federal

[5] National Organ Transplant Act, Public Law 98-507, 98th Cong. (October 19, 1984).
[6] 45 C.F.R. § 46.101.

department or agency but is subject to regulation as defined in § 46.102(e) must be reviewed and approved, in compliance with § 46.101, § 46.102, and § 46.107 through § 46.117 of [the Common Rule], by an institutional review board (IRB) that operates in accordance with the pertinent requirements of this policy."[7] It is relevant to note that research covered under the Common Rule also "may be subject to further appropriate review and approval or disapproval by officials of the institution."[8]

The Common Rule states that "*Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) Data through intervention or interaction with the individual, or (2) Identifiable private information."[9] By virtue of not being "living individual[s]," donors who are declared deceased by neurologic or circulatory criteria (see Chapter 1) fall outside of the protections of the Common Rule, and therefore obtaining permission from deceased individuals (or their surrogates) is not required for their participation in research. To be clear, even though the requirement of *informed consent* under the Common Rule does not apply to deceased donors, *authorization* for organ donation, even if the organs are used only for research purposes, is still required under the UAGA. The ethical principles inherent in the UAGA focus on respect for persons by honoring the decedent's determination of what should be done with his or her body after death (see Chapter 2).

A final rule[10] amending provisions of the Common Rule was promulgated on January 19, 2017, with an effective date of January 19, 2018 (*Federal Register*, 2017). The final rule "is intended to better protect human subjects involved in research, while facilitating valuable research and reducing burden, delay, and ambiguity for investigators" (*Federal Register*, 2017, p. 7149). The purpose of the new regulatory action is to promote research by asking human subjects to "assume risk to advance the research enterprise, which benefits society at large" (*Federal Register*, 2017, p. 7149). The revised definition of human subjects reads,

> Human subject means a living individual about whom an investigator (whether professional or student) conducting research: (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. (*Federal Register*, 2017, p. 7260)

[7] 45 C.F.R. § 46.101 (a)(2).
[8] 45 C.F.R. § 46.112.
[9] 45 C.F.R. § 46.102(f).
[10] This final rule of the Common Rule is not to be confused with the Final Rule that guides the structure and operation of the OPTN.

Even with this revised language, deceased donors are still not considered human subjects within the meaning of the Common Rule, although authorization for donation is still required for compliance with the UAGA. The Common Rule's regulations that are pertinent to transplant recipients are discussed in detail later in the chapter.

U.S. Food and Drug Administration Regulations

The U.S. Food and Drug Administration (FDA) has regulations pertaining to research on deceased organ donors that are similar to but not identical with those in the Common Rule. The corresponding definition in FDA regulations reads, "*Human subject* means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient."[11] FDA regulations do not specify whether one must be alive to be a human subject. Nevertheless, this language has been understood by ethics, regulatory, and legal communities to imply that deceased donors are not human subjects because they are neither "healthy humans" nor "patients," and it is strained to think they become a participant in research after death (Glazier et al., 2015; Rodrigue et al., 2016). However, significant confusion remains in the transplant community as to how to interpret the above language (Rodrigue et al., 2016). The committee interpreted the regulations to mean that neither the Common Rule nor FDA's human subjects research regulation applies to deceased organ donors even though the UAGA still applies to deceased donors. (Later in this chapter, consideration is given to whether and to what extent these regulations may apply to the transplant recipients of donor organs that have been a part of research.)

ORGAN DONATION: IMPROVING TRANSPARENCY AND PUBLIC TRUST IN THE PROCESS OF AUTHORIZING DONATION

UAGA and Donation

The 2006 UAGA identifies four distinct purposes of an anatomical gift: transplantation, therapy, research, or education (see Box 3-1). The problem the committee grappled with is the conjunction of "transplantation" and "research" or, more specifically, organs that are the subject of research, conducted either in a deceased donor or after organ recovery from a deceased donor, *and* then made available for transplantation. Making a gift for one of the four identified purposes (e.g., transplantation) does not in and of

[11] 21 C.F.R. § 50.3(g) and § 56.102(e).

Box 3-1 2006 UNIFORM ANATOMICAL GIFT ACT, SECTION 4, STATING WHO CAN MAKE AN ANATOMICAL GIFT

SECTION 4. WHO MAY MAKE ANATOMICAL GIFT BEFORE DONOR'S DEATH.
Subject to Section 8, an anatomical gift of a donor's body or part may be made during the life of the donor for the purpose of transplantation, therapy, research, or education in the manner provided in Section 5 by:

(1) the donor, if the donor is an adult or if the donor is a minor and is:
  (A) emancipated; or
  (B) authorized under state law to apply for a driver's license because the donor is at least [insert the youngest age at which an individual may apply for any type of driver's license] years of age;
(2) an agent of the donor, unless the power of attorney for health care or other record prohibits the agent from making an anatomical gift;
(3) a parent of the donor, if the donor is an unemancipated minor; or
(4) the donor's guardian.

SOURCE: NCCUSL, 2006, p. 17.

itself preclude using the gift for another purpose (e.g., research) unless the donor or surrogate has specified otherwise, such as opting out of the other purpose at the time of authorization.

This is made clear by Section 8(f) of the 2006 version of the UAGA[12]:

> (f) In the absence of an express, contrary indication by the donor or other person authorized to make an anatomical gift under Section 4, an anatomical gift of a part for one or more of the purposes set forth in Section 4 is not a limitation on the making of an anatomical gift of the part for any of the other purposes by the donor or any other person under Section 5 or 10. (p. 29)

Therefore, it is plausible to read this section of the UAGA as treating the authorization for *either* transplantation or research to constitute authorization for the type of research that is the focus of this report, i.e., organ donor

[12] See also comment to Section 8: "Under subsection (f) the donor's gift of a part for one purpose does not preclude another person from expanding the gift to include another purpose under either Section 5 or 10. For example, suppose the donor signs a document of gift stating: 'I give my kidney for transplantation.' Following the donor's death, an individual listed in Section 9 could expand that gift to include research in the event the kidney was not medically suitable for transplantation. The right to expand the purposes of the gift can be restricted by the donor" (NCCUSL, 2006, p. 31).

intervention research followed by transplantation.[13] Glazier and colleagues (2015) refer to this as a grey area in the law and argue that in such cases,

> both purposes (transplantation and research) should be authorized to comply with the UAGA and ensure that the gift is used consistent with the donor's intent. This is also consistent with the ethical directive to maintain the public's trust in the donation system and provide appropriate transparency as to how donated organs are used. As a matter of practice this can be achieved by confirming that a donor's authorization in a registry or an authorization form signed by an appropriate surrogate includes research use of gifted organs and tissues.
>
> It is important to recognize the donor's right under the UAGA to direct how the anatomical gift can be used. An organ specifically gifted only for transplantation purposes cannot be used for research without violating the UAGA (which includes criminal penalties for certain intentional violations). The OPO [organ procurement organization] and the transplant team, as custodians of the gift are responsible for ensuring that the organs are used only for the purposes authorized. (Glazier et al., 2015, p. 2254)

The committee believes that this ambiguity deserves clarification. As it stands, such ambiguity may be an obstacle in advancing innovative organ procurement and transplantation strategies. Thus, resolving these concerns will be key to improving the overall donation and transplantation system in the United States.

The UAGA discussion thus far has focused on authorization by the decedent. However, as mentioned in Section 4 of the Act, other individuals, such as next of kin, may also authorize a gift.[14] Most often in the cases

[13] Part of the difficulty lies in the lack of definitions of the four purposes. As the comment to Section 4 of the UAGA states, "The terms 'transplantation, 'therapy,' 'research,' and 'education' are not defined in this [act]. Rather, they are defined by their common usage in the communities to which they apply. In general terms, transplantation refers to the removal and grafting of one individual's body part into the body of another individual. Research is a process of testing and observing, the goal of which is to obtain generalizable knowledge, while therapy involves the processing and use of a donated part to develop and provide amelioration or treatment for a disease or condition. Education posits the use of the whole body or parts to teach medical professionals and others about human anatomy and its characteristics" (NCCUSL, 2006, p. 19). This seems to suggest a view that transplantation is one thing, research another, and never the two shall meet. But of course, the category that is the focus of this report is exactly where the two intersect. The separateness of the categories in the minds of the drafters is further reinforced by the sample gift authorizations that the UAGA authors review in their comments on Section 5 one of which has a check box for three configurations "Transplantation or therapy" versus "Research or Education" versus "Both" and the other with check boxes for "only transplantation and therapy," "only research and education," and "transplantation, therapy, research, or education" (NCCUSL, 2006, pp. 22–23).

[14] Details about which individual qualifies as a surrogate to make a gift are clarified in Section 9 of the UAGA.

where a surrogate authorizes the gift, the laws still apply in the same manner as when the donor him- or herself authorizes the gift, and thus the interpretation of the relevant laws remains the same.

One other section of the UAGA that has relevance to how authorization for donor intervention research should be approached is Section 11, which gives priority to transplantation or therapy over research or education (see Box 3-2). However, two ambiguities in the language complicate the interpretation of how to handle organ donor intervention research followed by transplantation under this Section. The first ambiguity is the language of Subsection (d):

> if there is more than one purpose of an anatomical gift set forth in the document of gift but the purposes are not set forth in any priority, the gift must be used for transplantation or therapy, if suitable. If the gift cannot be used for transplantation or therapy, the gift may be used for research or education. (NCCUSL, 2006, p. 39)

In the context of this report, the UAGA indicates that a gift specified for transplantation *cannot* be used for research (when also specified) unless it is impossible to use that organ for transplantation. This limitation raises the question whether conducting research on the donor or the donor organ when it will be followed by transplantation comports with or violates this rule. That is, would it be correct to say that the organ "was used for transplantation" under the first sentence of Subsection (d) or to say the organ "was used for research" under the second sentence of Subsection (d)? The second sentence only takes effect when the organ "cannot be used for transplantation," but the intended endpoint of organ donor intervention research is the act of transplanting the organ. Although the research and the transplantation are sequential in time due to necessity, they are a conjoined process. However, the organ might ultimately not be transplanted because (1) the research made the organ unusable; (2) the organ was unusable and was not repaired by the research; or (3) the organ is not transplanted because of other circumstances unrelated to the research. But in the case of donor intervention research, the intent of the research is to improve the transplant outcome for current and future transplant recipients.

The second ambiguity pertains to Section 11(f), which states that

> if a document of gift specifies only a general intent to make an anatomical gift by words such as "donor," "organ donor," or "body donor," or by a symbol or statement of similar import, the gift may be used only for transplantation or therapy, and the gift passes in accordance with Subsection (g). (NCCUSL, 2006, p. 39)

Box 3-2 2006 UNIFORM ANATOMICAL GIFT ACT, SECTION 11 STATING WHO MAY RECEIVE AN ANATOMICAL GIFT AND FOR WHAT PURPOSE

SECTION 11. PERSONS THAT MAY RECEIVE ANATOMICAL GIFT; PURPOSE OF ANATOMICAL GIFT.

(a) An anatomical gift may be made to the following persons named in the document of gift:
  (1) a hospital; accredited medical school, dental school, college, or university; organ procurement organization; or other appropriate person, for research or education;
  (2) subject to subsection (b), an individual designated by the person making the anatomical gift if the individual is the recipient of the part;
  (3) an eye bank or tissue bank.

(b) If an anatomical gift to an individual under subsection (a)(2) cannot be transplanted into the individual, the part passes in accordance with subsection (g) in the absence of an express, contrary indication by the person making the anatomical gift.

(c) If an anatomical gift of one or more specific parts or of all parts is made in a document of gift that does not name a person described in subsection (a) but identifies the purpose for which an anatomical gift may be used, the following rules apply:
  (1) If the part is an eye and the gift is for the purpose of transplantation or therapy, the gift passes to the appropriate eye bank.
  (2) If the part is tissue and the gift is for the purpose of transplantation or therapy, the gift passes to the appropriate tissue bank.
  (3) If the part is an organ and the gift is for the purpose of transplantation or therapy, the gift passes to the appropriate organ procurement organization as custodian of the organ.

This raises the question of whether "transplantation or therapy" as used in this section includes research followed by transplantation. Importantly, several states have already adopted laws that allow organs to also be used for research (in addition to transplantation) when only a general intent to make a gift has been authorized (Glazier et al., 2015).

In summary, the language of the UAGA is ambiguous concerning when it is permissible to conduct research on deceased organ donors or recovered donor organs that will be followed by transplantation.[15] The committee

[15] To be fair, there is an arguable work-around in the act itself. As a comment in Section 11 explains, "If a gift made under Section 4 is limited to transplantation or therapy by Section 11(e) or (f), procurement organizations could approach persons with a priority to make gifts under Section 9 to expand the purpose of the gift to include research or education and obtain their consent to use the gift for those purposes in the event the gift is unsuitable for transplantation or therapy." This seems to suggest that the OPO could approach a donor family and ask them to expand their gift to allow not just "transplantation" but "research followed by

(4) If the part is an organ, an eye, or tissue and the gift is for the purpose of research or education, the gift passes to the appropriate procurement organization.

(d) For the purpose of subsection (c), if there is more than one purpose of an anatomical gift set forth in the document of gift but the purposes are not set forth in any priority, the gift must be used for transplantation or therapy, if suitable. If the gift cannot be used for transplantation or therapy, the gift may be used for research or education.

(e) If an anatomical gift of one or more specific parts is made in a document of gift that does not name a person described in subsection (a) and does not identify the purpose of the gift, the gift may be used only for transplantation or therapy, and the gift passes in accordance with subsection (g).

(f) If a document of gift specifies only a general intent to make an anatomical gift by words such as "donor", "organ donor", or "body donor", or by a symbol or statement of similar import, the gift may be used only for transplantation or therapy, and the gift passes in accordance with subsection (g).

(g) For purposes of subsections (b), (e), and (f) the following rules apply:
(1) If the part is an eye, the gift passes to the appropriate eye bank.
(2) If the part is tissue, the gift passes to the appropriate tissue bank.
(3) If the part is an organ, the gift passes to the appropriate organ procurement organization as custodian of the organ.

(h) An anatomical gift of an organ for transplantation or therapy, other than an anatomical gift under subsection (a)(2), passes to the organ procurement organization as custodian of the organ.

SOURCE: NCCUSL, 2006, pp. 38–39.

considered several potential approaches to rectify this ambiguity. One option would explicitly add research followed by transplantation as an additional purpose for donation in the UAGA and explicitly recognize that the donor or surrogate can authorize donation for the purposes of transplantation, research followed by transplantation, therapy, research, or education. If such a change were made, then when the donor or surrogate specified transplantation but not research followed by transplantation, the organ would not be available for organ donor intervention research. Such an approach would maximally empower the individual authorizing donation to express his or her preferences, but it could potentially overload the individual with too many choices and engender choice paralysis (Iyengar and Lepper, 2000). The committee was concerned that many potential donors

transplantation." It is a unclear whether the drafters intended for this provision to be used in this way because they included the proviso "in the event the gift is unsuitable for transplantation or therapy," which is not true in the type of research that is the subject of this report.

would inaccurately interpret the term "research followed by transplantation" to involve objectionable manipulations of the body and thus refuse to participate in research that they would otherwise want to participate in if they fully understood what the actual research entailed and its potential benefit to the organs, to the recipients of these organs, and to the field of transplantation. Because much of the authorization occurs at departments of motor vehicles (DMVs),[16] it would also impose burdens on those who work at those institutions to be prepared to counsel those considering donation about the differences between authorization for transplantation and authorization for research followed by transplantation. The committee also recognized, based on past experience, that amending the UAGA to explicitly discuss the category of research followed by transplantation and securing the wide adoption of the revised version would be no easy task.

Another option that the committee considered is to amend the UAGA to explicitly recognize that when the potential donor or the surrogate does not specify otherwise, the authorization for transplantation should be treated as also encompassing authorization for research followed by transplantation. If such an approach were taken, the next revision of the UAGA could explicitly recognize that authorization for transplantation also authorizes research followed by transplantation. This option would be desirable if one believed that when potential donors or surrogates authorize transplantation, they are seeking to make a gift of life, and research followed by transplantation is aimed at making such a gift of life more effective, without foreseeably compromising the quality of the gift of the specific organ. While there may be some potential donors who would be comfortable with donation for transplantation but not with donation for research followed by transplantation, such donors could explicitly state that their donation is for transplantation only. To ensure transparency and respect for each individual's right to decide, donors would need to understand that they have this option and would need to be provided with opportunities to learn more about organ donor intervention research and to be informed that the aim of this research is also to transplant the organs. Explicit information would need to be widely disseminated (including through DMVs, registries, and other sources of organ donation information) so that donors would be aware that by authorizing transplantation they would also be authorizing research followed by transplantation. In this way, those individuals who may be concerned about the research use of their organs (followed by transplantation) can clarify what they do and do not want to authorize.

In exploring these options the committee did not identify empirical evidence that quantified the public's sentiment on these options. More work

[16] These agencies have varying names across states and the acronym DMV is used here to simplify the discussion.

needs to be done to learn about the strengths and limitations of each of these options and to determine how best to provide potential donors and surrogates with clear choices that move the field of organ transplantation forward in saving and improving lives. Specifying the rules would bring much needed clarity to the UAGA, protect OPOs and transplant teams from the risks of operating in a legal "grey zone," and provide a set of clear default rules for donors so that they can understand what will happen based on what kind of gift they authorize.

There are other issues regarding the UAGA and research followed by transplantation that need clarification. For those individuals or surrogates who indicate a general intent to donate but do not indicate a specific purpose for that donation, the committee concludes that authorization for donation should be treated as also encompassing authorization for research followed by transplantation. Several states already have laws in place that go in this direction in that a general intent to donate authorizes transplantation and also that it authorizes research if the organ cannot be used for transplantation (Glazier et al., 2015). The UAGA could make this explicit and note that the general intent to donate would authorize research followed by transplantation.

First Person Donation: Individuals Providing Authorization

The most common occasion on which an individual specifies preference for being an organ donor is at the time of obtaining or renewing a driver's license at a state DMV. There are 53 donor registries through these agencies (i.e., in each of the 50 U.S. states, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands) (HRSA, 2017). In addition, Donate Life America operates a donor registry at the national level (Donate Life America, 2017).

Although the practice of providing authorization for organ donation at a DMV may be perceived as standardized, it is hardly systematic or nationally uniform. The committee obtained and reviewed the organ donation authorization forms of 26 different DMVs (25 states and the District of Columbia). These forms were ones that were accessible through the DMV websites. Wide variation was seen in how organ donation was addressed in these forms (see Box 3-3 for select examples of the variation). Furthermore, there can be a lack of communication between DMVs and hospital databases and a lack of sharing the information across state lines (e.g., if an individual registered in one state but died in another state, it may be difficult to ascertain whether the individual chose to be an organ donor). As a result, an individual's intention to donate could be missed because the established systems do not always allow for effective coordination and communication among institutions.

Box 3-3 QUESTIONS USED BY SELECT STATE DEPARTMENTS OF MOTOR VEHICLES TO OBTAIN AUTHORIZATION FOR ORGAN DONATION

ALABAMA
Organ Donor (circle one): Yes No

CONNECTICUT
Do you want to be in the organ/tissue donor registry?
(check one) ___Yes ___No
**If yes, you are agreeing to be a donor and the designation will be on your license.*

HAWAII
Do you wish to be an organ/tissue donor? ___Yes

NEW YORK
To enroll in the NYS [New York State] Department of Health's [DOH's] Donate Life Registry, check the "yes" box and then sign and date below. You are certifying that you are: 18 years or older; consenting to donate all of your organs and tissues for transplantation, research, or both; authorizing DMV to transfer your name and identifying information to DOH for enrollment in the Registry; and authorizing DOH to allow access to this information to federally regulated organ donation organizations and NYS-licensed tissue and eye banks and hospitals, upon your death. *"ORGAN DONOR" will be printed on the front of your DMV photo document.* You will receive a confirmation from DOH, which will also provide you an opportunity to limit your donation.

You must answer the following question: Would you like to be added to the Donate Life registry?
(check one) ___Yes (sign and consent below) ___Skip this question

Donor Consent Signature: → _____
Date: _____

OREGON
Do you want your license or ID card to show that you are an anatomical donor?
(check one ___Yes ___No)

SOUTH DAKOTA
___ In the event of my death, I would like to be an organ/tissue donor.
To remove an existing donor indicator on your card write "remove" here and initial _____.

TEXAS
Yes___ No___ Would you like to register as an organ donor?

WYOMING
(check one) ___Yes ___No Do you wish to join the organ and tissue donor registry? ***If under 18 years old, you must have your parent/guardian permission to be a donor.*
***The above minor has my permission to register as a donor:*
_____*Parent/Guardian signature*

These challenges are compounded by the fact that there is no standard practice for recording an individual's preferences for donating organs for the purpose of research, whether through a declaration at DMV or through another nongovernmental declaration. In fact, many DMV forms are silent regarding donation for the purpose of research: Only 2 out of the 26 forms that the committee reviewed had any mention of research related to organ donation. One such example—New York—is shown in Box 3-3. In instances where research is not specified, the OPO would need to get authorization for research from the surrogate because, as stated earlier in this chapter, the UAGA default legal provisions hold that if a person has agreed to be a donor with no further clarification about research, this authorizes transplantation or therapy only, and authorization must be obtained for using the gift for other purposes (i.e., the "grey area" referred to earlier in this chapter in the discussion of the UAGA).

OPOs and the Donate Life America registry provide information to the general public regarding organ donation through different media, including websites, brochures, handouts, and contact information for relevant organizations (e.g., OPOs, OPTN/UNOS, Association of Organ Procurement Organizations). However, there are no requirements for what information about organ donation options, including research, should be provided to individuals who are contemplating registering to be an organ donor. The lack of guidance and the need to be transparent with the public raise the question whether there should be federally mandated requirements for donor registries concerning what information must be provided at the time of registration, how questions of donation should be worded, and what information should be made available on websites, brochures, handouts, etc.

Processes for obtaining authorization for organ donation, including for what purposes the donated organ may be used, should be made more consistent across the United States. Such consistency would make the process simpler and more informative to the individual considering donation as well as making the process more useful to transplant professionals acting on that information. Importantly, if organ donor authorization processes were more uniform in offering all potential options, donor intent would be more transparent. Simplifying the process would mean that organizations acting as donor registries would use one simple set of language for providing information and obtaining authorization. Anyone considering donation would receive the same options and information for donation no matter where they registered. Establishing the same format, level of detail, options, and clear explanations would demonstrate transparency in the process presented to those determining whether or not to donate and whether to qualify their decision by permitting or refusing organ donor intervention research prior to transplantation. Full disclosure and transpar-

ency are essential for establishing and ensuring long-term public trust in organ donation and transplantation.

Parallel to this, and as a reinforcement, lay language informational content should be developed and provided to individuals considering the options for donation. Messaging and communication strategies regarding organ donation and donor intervention research need to be developed and thoroughly tested to meet the health literacy needs across the general public. It will be important to identify the potential benefits of transplantation with organs that have been the object of organ donor intervention research in awareness and educational programs about organ donation. This is particularly important for populations who may be suspicious of research because of a long history of biomedical research abuses (see Chapter 2). The committee concluded that the testing, development, and implementation of lay-friendly materials that explain donor intervention research and put it in the wider frame of increasing opportunities for organ transplantation will work toward improving transparency and public trust in the organ donation system.

The goal will be to have well-developed and standardized information templates that can be provided at the time that individuals register their decisions for donation, with an option to be referred to a website for more detailed information, etc. In addition, the information that each OPO receives on each potential donor should be uniform, which would make the entire donation and transplantation process more seamless. The committee recognizes that revising DMV forms, website links, and OPO informational content will be challenging but believes that particularly in this joining of organ donation and research—both areas that deserve careful consideration, participation, and endorsement by the general public—taking the time and placing an emphasis on communications and public information is critically important.

Additionally, attention needs to be placed on implementing a single national organ donor registry. To accomplish this will require extensive coordination and standardization. Model state legislation could be helpful in facilitating a merger of registries as could federal regulatory changes to centralize the management of this effort.

Surrogates Providing Authorization for Organ Donation and Research

Family involvement in the donation process is important for transparency and public trust, regardless of whether it is the donor or a surrogate who provides the authorization. The surrogate and family, who may bear the experience on a personal level for their lifetimes, can influence others regarding donation. When the donation process is managed well, it propagates trust and respect, which are critical to the donation and transplantation process (see Chapter 2).

Every donation scenario differs. Current practice varies from state to state and from OPO to OPO regarding informing the donor's family or other surrogate of a decedent's declaration of intent to be an organ donor and seeking the family or surrogate's permission for donation (Chon et al., 2014). When a potential donor has not provided authorization for donation or when there is no evidence of authorization for donation, a designated requestor approaches the surrogate, who has the choice of whether to provide authorization for donation, including any specific exclusions, such as certain organs that cannot be donated or certain purposes for which the organs cannot be used. Generally, designated requestors work for the local OPO, but in remote hospitals, the requestors may be trained by the OPO but not work for it. Requestors are often accompanied by hospital personnel who have been caring for the potential donor and family (LifeSource, 2011). These requestors assume primary responsibility for the organ donation process. A requestor may use different styles and formats in discussing donation and research with surrogates, depending on the specific circumstances surrounding an individual donor (LifeSource, 2011), so the information provided to different surrogates can vary.

The discussion of organ donation with a surrogate often occurs at a time when the surrogate's cognitive capabilities are stressed because of the sudden crisis of a friend's or family member's death, which is often unexpected. This sensitive situation is made even more complex if the designated requestor must explain both donation and research options under time constraints and determine on a case-by-case basis how much information is enough, too much, or too little. This can put the organ recovery team at risk of applying undue and inappropriate influence on the family. Planning ahead by having materials for the requestor to share about the inclusion of donor research as part of transplantation can help to reduce stress about decisions for donation.

Authorization for Pediatric Donors

Minors made up approximately 9.4 percent of all deceased organ donors in the United States in 2016 (OPTN, 2017b). The committee considered organ donor intervention research as it pertains to pediatric donors and concluded that pediatric donors should be included as potential participants in donor intervention research unless excluded because of certain weight or size criteria. For minors—generally those who are less than 18 years old—the authorization process for organ donation allows the minor's parents or guardian to make decisions about post-mortem organ donation.

For older children who die, parents or guardians may be able to incorporate what they know about the minor's values and preferences into their

decision about organ donation. It is possible, for example, that a minor may have had a discussion with his or her parents regarding donation, perhaps as a result of a program on organ donation that the minor experienced in school (Cárdenas et al., 2010; Li et al., 2013). Thus, the parents or guardian may know whether their minor child would or would not have wanted to be a donor. This can influence their decision whether to provide authorization for their child's donation, a fact that reinforces the need for educating the public regarding organ donation and related research.

Providing Organ Donor Intervention Research Findings to Families, Surrogates, and the Public

Providing basic information about transplant recipients to the families and surrogates of deceased organ donors is common when the provision of such information has been agreed upon by both parties. In 2011, a task force of stakeholders convened to make recommendations to help standardize the information that is provided (OPTN, 2017c). Similarly, findings from organ donor intervention research should also be shared with organ donor surrogates and families in addition to being shared with the public. Providing the research findings in aggregate form will increase transparency about the research while also demonstrating the societal benefit of organ donor intervention research.

RECIPIENTS OF RESEARCH ORGANS: IMPROVING CONSENT AND ENSURING PROTECTIONS

In accord with the policies of OPTN and with other standards of medical care, transplant recipients go through a clinical consent process before undergoing transplant surgery. Beginning at the time of initial intake, through the process of being added to the transplant waitlist, and at the time of a specific organ offer, discussions between the potential transplant recipient and the clinical transplant coordinator, the transplant surgeon, and other clinicians focus on the risks, the processes, and the opportunities for transplantation, including the options regarding increased risk organs. In being added to the transplant wait list, potential transplant recipients are notified about OPTN policies and processes regarding the collection of a standard set of data that are used in de-identified form for transplantation reporting and statistics. In the context of this report, the committee focuses on the added complexities involved in being the recipient of an organ that has been the target of a research intervention prior to transplantation (with the intervention occurring while the organ was in the deceased donor or after being removed from the donor but prior to transplantation) or the recipient of a non-target organ that was potentially exposed to the research

intervention that occurred prior to removal of the organs from the donor. This section examines the effective and ethical implementation of the laws that ensure human research subject protections with particular attention to the following questions:

- Are recipients of research organs human research subjects?
- What are the issues regarding informed consent?
- How can the informed consent processes use risk stratification?
- How can consent be most effectively obtained given the time-sensitive nature of these decisions?
- What are the issues for post-transplant follow-up?

Recipients of Research Organs: Are They Human Research Subjects?

As noted earlier in the chapter, the new revision to the Common Rule states two criteria for being designated a human subject of research and thus being afforded a set of highly regulated research protections:

> *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research: (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. (*Federal Register*, 2017, p. 7260)

Even though deceased organ donors are not considered human subjects in research as defined by the Common Rule and FDA regulations (see discussion earlier in this chapter), there is still debate about whether recipients of organs targeted in donor intervention research and recipients of non-target organs exposed to donor intervention research are human subjects under the regulations. The committee acknowledged the range of types of organ donor intervention research interventions and considered several research scenarios in looking at these issues.

For three types of studies, the decision about human research subjects is not controversial:

1. Studies using de-identified data—As long as the use of de-identification data meets the Common Rule's requirements, the research participants would not be defined as human research subjects.
2. Studies that explore outcomes only prior to transplantation—These types of studies collect data on and analyze the effects of interventions on the organs themselves prior to transplantation, without

evaluating how the transplanted organs—target or non-target—function in recipients and without collecting or examining any data from the transplant recipient(s) about patient or graft function after transplantation. Because the recipients of target and non-target organs involved in these types of studies would not meet the Common Rule's definition of a human subject, obtaining research informed consent from the recipients would not be required. However, because research is part of the organ's clinical history, maintaining transparency and trust in the organ donation and transplantation process will require that the potential transplant recipient be informed about the research intervention as part of the clinical informed consent process for transplant surgery. Additionally, the committee is concerned that these types of studies may be missing opportunities to increase the knowledge about how to improve organ quality and function (for target and non-target organs) and would urge the data be collected and studied where feasible, which would require appropriate human research protections.

3. Studies that collect additional patient data or biospecimens—These studies would collect data from transplant recipients beyond the standard-of-care follow-up. For example, blood draws, biopsies, or other measures of organ function could be required as part of the research protocol in order to assess the effectiveness of the research intervention. In these cases, as per the Common Rule regarding data collection, the transplant recipients would be deemed to be human research subjects and the single IRB (see Chapter 4) would oversee the implementation of human research subjects protections. As discussed below, the extent of the protections may vary based on the risk level of the intervention as determined by the IRB. If the research intervention were conducted in the deceased donor prior to removal of the organs then there would be the possibility of all organs being affected and therefore, all recipients of target or non-target organs would be human research subjects. If the research intervention were conducted on a specific organ after its removal from the body and prior to transplantation, then only the recipient of the intervention organ could be affected and only he or she would be a human research subject.

There is less clarity and more controversy about a fourth type of study in which some intervention on the donor or donor organ has been done for research purposes but the only data from organ recipients that would be collected are part of standard-of-care follow-up (Carome and Wolfe, 2016; Heffernan and Glazier, 2017). In other words, the standard-of-care follow-up data are being used both for clinical *and* for research purposes. In these

cases, much of the determination of whether the transplant recipients are research subjects hinges on the wording of the Common Rule regarding research data and noting that data of concern are those obtained by investigators "through intervention or interaction with the individual."[17] The Common Rule defines "intervention" to include "both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes."[18] Because organ donor intervention research modifies organs and assesses the function, efficacy, and safety of those modified organs in transplant recipients, the committee believes that the subject or the subject's environment is being manipulated for research purposes. As noted in the Common Rule, when data generated from a research intervention are linked to the transplant recipient, or identifiable private information is being used or analyzed, the transplant recipient qualifies as a human research subject. The recipient's clinical consent, which applies, for example, to his or her acceptance of an increased risk organ, would not be sufficient for acceptance of a research organ when data from the recipient will also be linked to the intervention performed on the organ prior to transplantation, even if those data were collected as part of standard of care. In these cases, the committee believes that the single IRB should require informed consent for research participation, unless it determines in appropriate cases that the criteria for alteration or waiver of informed consent are met.

Figure 3-1 summarizes the above discussion and includes issues regarding levels of risk and informed consent that are discussed in the following sections of this chapter.

Recipients of Research Organs: What Are the Issues Regarding Informed Consent?

Concerns have been expressed that treating recipients of transplanted research organs as human subjects would create nearly insurmountable logistical problems because allocation of the organs occurs after the research intervention has been administered (Heffernan and Glazier, 2017).

These concerns focus on the difficulty of obtaining prior IRB approval in the absence of knowing which institutions will receive the research organs and on the difficulty of obtaining advance research-related informed consent from potential recipients. While such possible consequences and barriers are certainly a reason for caution, pragmatic considerations alone should not dictate the outcome of legal, regulatory, and ethical analysis. In fact, treating recipients of transplanted research organs as human subjects

[17] 45 C.F.R. § 46.102(f).
[18] 45 C.F.R. § 46.102(f).

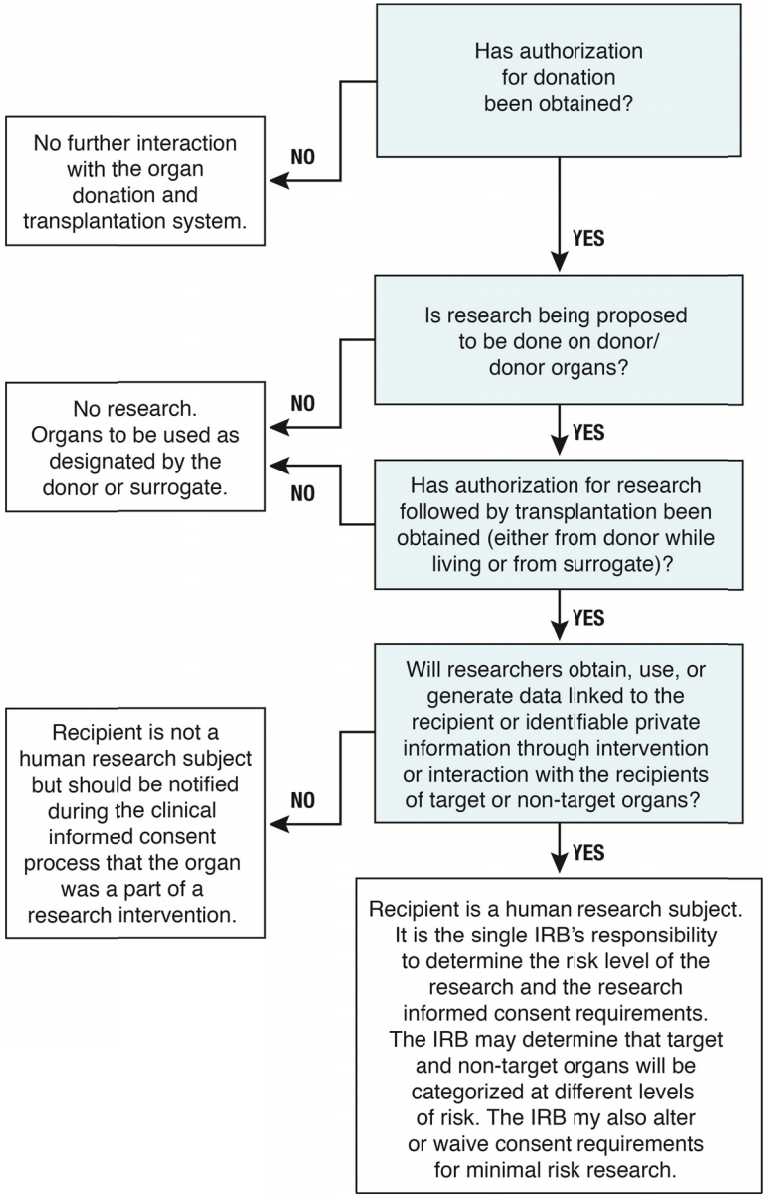

FIGURE 3-1 Research authorization and consent decision points.
NOTE: IRB = institutional review board.

need not create insurmountable obstacles to organ donor intervention research. Thus, the committee, in line with several developments in human subjects research, recommends a single IRB review for these studies (see Chapter 4). The committee also proposes—and develops in a subsequent section of this chapter—a two-step consent process and other practices that can expedite the process of obtaining research-related informed consent. Moreover, as discussed below, in some instances waiver or alteration of informed consent may be a possibility for some kinds of protocols.

The Common Rule lays out several criteria for IRB approval of research involving human subjects:

1. "Risks to subjects are minimized"
2. "Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result"
3. "Selection of subjects is equitable"
4. "Informed consent will be sought from each prospective subject or the subject's legally authorized representative"
5. "Informed consent will be appropriately documented"
6. "When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects"
7. "When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data"[19]

Moreover, if any of the prospective subjects "are likely to be vulnerable to coercion or undue influence," other regulations require additional safeguards.[20] Vulnerable populations include children, prisoners, etc.

The Common Rule also delineates several general requirements for an individual's or a surrogate's consent to research participation. It mandates that the IRB require researchers to disclose that the study involves research; to describe "any reasonable foreseeable risks or discomforts"; to describe any reasonably expected benefits to the subject or to others; to disclose "appropriate alternative procedures or courses of treatment, if any"; to indicate the extent of the protection of confidentiality; to specify that participation in research is voluntary; etc.[21] When appropriate, other elements of information for consent shall be provided, such as the additional costs to the subject and any effects of the subject's decision to withdraw from the research.[22] The alteration of some elements of informed consent or even a

[19] 45 C.F.R. § 46.111(a).
[20] 45 C.F.R. § 46.111(b).
[21] 45 C.F.R. § 46.116(a).
[22] 45 C.F.R. § 46.116(b).

waiver of the requirement of informed consent can be approved by the IRB under some stringent circumstances to be discussed below.

Pediatric Considerations

There are reasons to include children in donor intervention research, the most salient being that organs are scarce and children should not be excluded from receiving such organs if a transplant is deemed to be in their best interest. There are cases where research is done simultaneously with adults and children, and regulations from the 1990s and 2000s encourage an earlier enrollment of children.[23]

For recipients who are minors, parents or legal guardians are legally empowered to provide consent for transplant and research. While obtaining child assent is often encouraged, the federal regulations allow an IRB to make a determination on whether the minor's assent can be waived.[24] Again, the committee thought that these determinations should be made by the single IRB, proposed in Chapter 4, in light of the time constraints and life-saving therapies that are being offered. One could imagine a decision to waive assent requirements up front but to inform the minor at some future time in order to show respect for the minor's increased autonomy.

Considerations Regarding Non-Target Organs

The committee believes that the IRB will need to carefully consider the issues regarding non-target organs in order to ensure respect for the recipient, maintain confidence in the transplantation system, and gain knowledge about the impact of donor research interventions. In research that aims to improve donor outcomes, the effects that interventions aimed at a target organ may have on other organs must be included in the risk–benefit calculation when deciding whether the research may go forward (see the discussion of beneficence and fairness in Chapter 2). As with all recipients of organs involved in organ donor intervention studies, recipients of non-target organs (whether deemed to be human research subjects or not) need to be informed that they are receiving an organ that has been part of a research study.

Second, because this research aims to increase the quality and quantity of organs that will be viable for transplantation, it is critical to gain knowledge about whether or not there is an impact of the intervention on

[23] Best Pharmaceuticals for Children Act, Public Law 107-109, 107th Cong. (January 4, 2002). Food and Drug Administration Modernization Act of 1997, Public Law 105-107, 105th Cong. (November 21, 1997).

[24] 45 C.F.R. § 46.408(a).

the non-target organs and the extent of that impact. Researchers should be encouraged to analyze data on non-target organs in order to assess whether interventions targeted on a specific organ have effects on other organs. In some cases, data that are routinely collected as part of normal transplantation follow-up protocols might be sufficient, but, for other studies, additional data collection may be important.

Third, the committee acknowledges that the level of risk to the recipient may differ among the target and the non-target organs in the same study. As will be discussed in the following section, the informed consent process may be altered by the IRB depending on the risk level.

How Can the Informed Consent Processes Use Risk Stratification?

Concerns have been raised that requiring informed consent for organ donor intervention research that poses no more than minimal risk is too burdensome under the time constraints imposed by the transplantation process. Under the Common Rule, "an IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent."[25] Given the time constraints that are present when allocating deceased donor organs to transplant candidates (see Chapter 1), altering the elements of informed consent for transplant recipients might be useful and appropriate when donor intervention research poses no more than minimal risk to the recipient. This section examines the potential for alteration or waiver of informed consent depending on risk level and discusses the need for a common vernacular regarding levels of risk.

Research That Poses No More Than Minimal Risk

The Common Rule states that the requirement for informed consent can be altered or even waived as follows:

> An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:
>
> (1) The research involves no more than minimal risk to the subjects;
> (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
> (3) The research could not practicably be carried out without the waiver or alteration; and

[25] 45 C.F.R. § 46.116(d).

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.[26]

The committee concluded that organ donor intervention research that entails no more than minimal risk may meet these four criteria under some circumstances. Although there is significant risk in becoming a transplant recipient in general, here "minimal risk" refers only to the additional risks that could be incurred by the research participation itself. The Common Rule defines minimal risk as existing when "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."[27] The committee did not render judgment as to whether trials that randomize transplant recipients to different standards of care—as in comparative effectiveness research—should generally be classified as minimal risk; instead, it left this for the IRB to determine on a study-by-study basis.

It is important to note that while the determination of minimal risk is necessary for a waiver or alteration of informed consent for research, it is not sufficient. Criteria 2, 3, and 4 identified above must also be met. Regarding criterion 2, the clinical consent information provided to the potential recipient could provide the needed information on the minimal risk research protocol to the recipient. Given the deleterious effects of delay in allocating deceased donor organs, researchers may be able to make the case that criterion 3 regarding practicability applies in some studies where the intervention poses no more than minimal risk. Criterion 4 requires that recipients be given additional information at a later time. Given that transplant recipients are followed closely after transplantation, it may be possible to provide some types of information after participation (including sharing aggregate results) but as the Common Rule recognizes it will be for the IRB to determine what is appropriate.

The committee concluded that the single IRB (see Chapter 4) is the body that should review and assess the systematic risk appraisal conducted by the research investigators and should determine whether an alteration or waiver of consent is appropriate for a given study. This determination should be made on a study-by-study basis. The Common Rule allows IRBs to determine that consent can be totally waived for certain studies deemed to be of minimal risk. If the single IRB makes the decision for a waiver in an organ donor intervention research study, the committee emphasizes the need to reveal the organ's research history (for target and non-target organs) during the clinical informed consent process because

[26] 45 C.F.R. § 46.116(d).
[27] 45 C.F.R. § 46.102(i).

that is part of its clinical history and ensuring that the potential transplant recipient knows the full history is required by the ethical principle of respect for persons (see Chapter 2).

For minimal-risk research, the Secretary's Advisory Committee on Human Research Protections has endorsed less burdensome approaches to obtaining consent (such as oral consent) that might be appropriate (OHRP, 2015). While the candidate would sign a standard clinical consent form for organ transplantation, either a brief consent form or a verbal consent could be adequate for this type of research participation under some circumstances. Again, the committee concluded that the single IRB (see Chapter 4) is the body that should determine how consent will be documented for studies of minimal risk (e.g., brief consent with certain elements waived or verbal consent with certain elements waived).

Questions arise as to whether research informed consent could be justifiably waived for research participants who are randomized to a purely observational arm or an arm that delivers the standard of care for the center where the transplant is being performed. After all, the organs that these individuals receive would not differ from what they would have received had they not been enrolled in research (i.e., they are the control arm), and the data collected would not differ from the standard data collected from all transplant recipients. The committee leaves it to the judgment of the single IRB, on a study-by-study basis, to determine whether it is appropriate to approve an alteration of the elements of informed consent or even waive the requirement for research informed consent for such research participants. The IRB should also determine whether respect for the rights and welfare of these transplant recipients requires that they be informed of their participation at some future time (Criterion 4 above).

Research That Poses More Than Minimal Risk

In the cases of research that poses *more than minimal risk*, federal regulations do not permit the alteration or waiver of research informed consent, and researchers must use the standard consent processes for clinical trials as defined in the Common Rule.[28] Among other things, candidates should be given a full description of the research intervention being investigated, the possible risks and benefits of the research, the extent to which additional follow-up will be needed, and the degree of invasiveness that follow-up would entail. This information should be provided so that the candidate can use the information in his or her decision about whether to accept the organ and participate in the research.

[28] 45 C.F.R. § 46.116 and § 46.117.

Facilitating the Risk Discussion: Developing a Common Vernacular

As noted in Chapter 1, time is a critical factor for preserving a donor organ prior to transplantation. During the short time window for carrying out a transplantation before the organ loses its viability, it is unrealistic to expect members of the transplant team and transplant candidate to fully digest the data and clinically relevant information necessary to understand the scientific rationale and exact potential risk for clinical harm to a recipient of a research organ. Therefore, a common vernacular should be developed to (1) inform transplant teams about the degree of risk for harm that their patients can anticipate if they accept a specific research organ (target or non-target); and (2) inform potential recipients, in terms they can quickly and easily understand, about the risk for harm that they assume if they accept a research organ.

In considering what that common vernacular might be, the committee took guidance from discussions on binning genomic information before providing it to patients (Berg et al., 2011; NCHS Board of Scientific Counselors, 2012). The goal of those discussions was to create a categorical, patient-driven, and streamlined approach to the clinical evaluation of novel genomic variants and to facilitate patient engagement, with consideration given to "how to determine and operationalize criteria for clinically relevant genetic findings with a dire duty to warn threshold" (NCHS Board of Scientific Counselors, 2012). One solution was to bin genomic information into three separate categories (NCHS Board of Scientific Counselors, 2012). In follow-up on that same model, Berg and colleagues (2011) suggested that binning would allow clinicians to create categories delineated by scope of clinical utility into which genetic variants can be assigned on an a priori basis.

For purposes of informing transplant teams and candidates about research organs (target and non-target), the committee suggests that the Donor-Research Oversight Committee and the single IRB, described in Chapter 4, explore categorizing each study's potential to cause harm to recipients. Studies could, for instance, be categorized into three bins: (1) no more than minimal risk, (2) at most, a minor increase over minimal risk, or (3) more than a minor increase over minimal risk. Bins may be referred to using a common risk scale of 1+, 2+, 3+. Organs categorized as minimal risk would be 1+, while organs categorized as significant risk for their recipients would be 3+.

A significant advantage of a routinized scale would be that it would allow transplant centers to learn their transplant candidates' risk tolerance for research organs and note this at the time of listing using a standardized tool. Transplant candidates would only be offered organs that fit their risk tolerance preferences, thus further facilitating efficiency in the allocation of donor organs without compromising transplant candidates' preferences.

Importantly, transplant candidates should have the opportunity to alter their risk preferences at routine intervals, just as they can change their preference about accepting organs from increased risk donors. This is a process that will need to evolve as OPTN and transplant centers, in conjunction with the research oversight structure recommended in Chapter 4, explore how best to inform transplant candidates about research organs, and identify ways to convey risk.

How Can Consent Be Most Effectively Obtained Given the Time-Sensitive Nature of These Decisions?

The limited window of time during which an organ is viable for transplantation and during which many steps in the transplantation process must take place (see Chapter 1) necessitates careful consideration about how to most effectively inform transplant candidates about organ donor intervention research. Additionally, transplant candidates receive a wealth of information from the time of intake through the time of discussing a transplant organ offer and need to have the time to fully learn about organ donor intervention research and make a determination about whether they may wish to receive a transplant organ that has been part of this research.

In order to find a balance between the laws and regulations relevant to organ donor intervention research and the need to ensure that organs do not become unusable due to an excessive elapse of time, the committee proposes the following two-stage process for obtaining consent from transplant candidates who could receive a target or non-target research organ. In this process, the first stage would involve providing information on donor intervention research and would ask the transplant candidate to make a decision on whether they would want to consider receiving a research organ, which could involve the collection of research data (see details below). This first stage is part of the clinical consent process that begins at the time of intake and continues through wait listing. The second stage would occur when an organ is being offered to the transplant candidate and would follow research informed consent processes as determined by the single IRB. The committee considered other options that would require revisions to the Common Rule but concluded that the proposed two-stage process should stay within current human research subjects protection regulations and that this process offers the best opportunities to

- fully inform transplant candidates about organ donor intervention research at a time when they can consider the risks, benefits, and alternatives in depth,
- provide a thorough informed consent process for participation in research, and

- allow the process to be conducted as expeditiously as possible by only doing the more in-depth informed consent processes with those candidates who have expressed an interest in receiving a research organ.

First Stage: Informing Transplant Candidates About Donor Research at the Time of Intake or Listing

It is common for clinicians to discuss increased-risk organs with transplant candidates to identify whether each candidate wants to be approached when such organs are available for transplantation (Seem et al., 2013). These conversations typically occur *at intake*—that is, when patients are evaluated as potential transplant candidates—or *at listing*—that is, when patients are placed on transplant waiting lists. At these same times, clinicians could provide information on donor intervention research and ask whether the transplant candidate wants to be considered for a research organ (target or non-target organ). The information provided would include an overview of organ donor intervention research and an explanation of the range of research studies that might occur during the time the transplant candidate is waiting for an organ. The information provided to the patient would not include details on specific research protocols as this information would likely not be available. These initial discussions would enable transplant candidates to become familiar with the possibility of receiving research organs at a time when they are not pressed to make an urgent decision about a specific organ. It will also give each transplant candidate the opportunity to think about whether he or she may be interested in considering a research organ at a later time if one became available (while being able to opt out later), similar to deciding whether to consider increased-risk donor organs. The discussion would need to lay out the ramifications of the transplant candidate's decision regarding research organs and note that at any point while on the transplant waiting list, the transplant candidate can change his or her decision regarding whether to be notified about a research organ.

At this stage, each transplant candidate should be informed that

1. Opting out of being notified about research organs signifies that the transplant candidate will not be told about research organs when those organs become available.
2. Opting in to being notified about research organs:
    - Signifies that the transplant candidate will be told when a research organ becomes available and will go through an IRB-approved consent process.
        - If the research is determined to pose more than minimal risk, the transplant candidate will go through a full in-

formed consent process used for human subjects in research as approved by the IRB.
    - If the IRB determines that the research is no more than minimal risk, it may approve the alteration of elements of informed consent (see discussion of alteration of consent above).
    - If the research does not involve the collection and analysis of data on follow-up outcomes, then the transplant candidate will be asked for clinical consent, similar to what is done for increased-risk donor organs.
- Involves decisions about whether to accept or decline a specific research organ at the time it becomes available.
    - If the candidate declines a specific research organ at any time, he or she can still consider other research organs at later times.

3. Each candidate's decision in this phase of the process of whether to opt in to considering a research organ would be recorded in UNet^{SM}, the OPTN database housing organ transplant waiting list data. This database is used by OPTN/UNOS to make determinations regarding organ allocations, and the notation on willingness to accept a research organ would be one of many factors used in determining the allocation for a given research organ.
4. At any time, the transplant candidate can change her or his mind with regard to opting in or opting out of receiving a research organ.
5. Going forward, the transplant candidate's willingness to be approached about receiving a research organ will be reassessed at the same time(s) that their transplant team re-assesses their willingness to receive increased risk donor organs that are not part of research protocols.
6. If the transplant candidate does accept a research organ, she or he can opt out of participating in any post-transplant follow-up specific to the research study, but the organ would not be removed unless determined to be causing harm, and the routine data collected from all transplant recipients would continue to be collected and used as permitted by OPTN policies.

During these discussions of donor intervention research, each transplant candidate should be given the opportunity to opt out of being offered research organs that become available in the same way that they can opt out of being approached when increased risk organs become available. The transplant candidate should also be given the opportunity to be offered research organs that, in the opinion of their transplant team, may be compatible with the degree of risk that the transplant candidate is willing to

tolerate. (This process on stratifying risks is further described above and would require that the transplant team thoroughly evaluate each transplant candidate's risk tolerance for personal harm as the result of accepting a research organ.) Allowing transplant candidates to opt out of being offered research organs or to agree to consider only organs that fit their risk tolerance will reduce the time that organ placement and transplant teams spend allocating organs to candidates and thus reduce the likelihood of delays to allocation which may result in the organ being injured and rendered unusable for transplantation.

While transplant candidates have the right to opt out of being approached about research organs, it is incumbent upon clinicians and transplant programs to fully inform transplant candidates and make sure that they understand the consequences of opting out. For example, clinicians should make sure that candidates understand that opting out of considering research organs may lengthen the time it takes for them to get a transplant because of the limited supply of organs and the challenges of finding an appropriate organ. Clinicians should inform transplant candidates that some research organs may have been procured in ways that are consistent with current standards of care, with the research designed simply to determine which standard procedures might best promote transplant success. Although this discussion about considering a research organ would first occur at intake or at listing, it should not be a one-time-only discussion. The discussion should be revisited at regular intervals with the candidate's transplant team so that the candidate has opportunities to change his or her decision.

Second Stage: At the Time of Organ Offer for Transplantation

If a potential candidate is willing to consider receiving a research organ, then when the time arrives for the candidate to be offered a specific research organ, details on the research protocol would be provided and the appropriate level of informed consent, as determined by the single IRB, would be obtained. The clinician and clinical transplant coordinator would be trained in human subjects research protections, would have information on the specific research protocol, and would work to succinctly describe the research intervention, answer the potential recipient's questions regarding research participation, and ensure that the research informed consent process is conducted as required.

The level of information provided in this second stage would not be unusual and can be done expeditiously. As is standard practice, transplant teams inform potential recipients about the nature of the candidate organ (e.g., the approximate age of the donor, the health of the donor, the mode of the donor's death) and whether the organ donor has been designated as

being of increased risk (OPTN, 2017a). Transplant teams give potential recipients this information so that they can decide whether accepting the available organ is in their best interest. In much the same manner, clinicians should inform transplant candidates who have expressed an interest in potentially considering research organs when an organ is part of a research study so that the candidates can factor this information into their decision about whether to go forward with the transplantation of a particular organ. In many cases it will be appropriate for the transplant clinicians to also make a recommendation to the candidate about whether, in their judgment, accepting a particular organ would be in the candidate's best interest. Clinicians will have access to the details of the study protocol through UNet^{SM} and through the registry of donor intervention studies (see Chapter 4), and if there are questions about the research study protocol, clinicians working directly with the potential recipient can be in touch with the research study staff.

As discussed above, the second stage for considering a research organ has two pathways defined according to the risk level of the research: (1) research that poses no more than minimal risk, and (2) research that poses more than minimal risk. Use of a common framework for discussing risks with transplant candidates will be important in moving the decisions forward as expeditiously as possible.

What Are the Issues for Post-Transplant Follow-Up?

Regardless of whether a transplant recipient receives an organ in the context of no-more-than-minimal-risk research or greater-than-minimal-risk research, at the time of any research-specific follow-up or procedures, recipients should be informed that they can withdraw from research-specific follow-up at any time. They can withdraw from extra data collection and extra interventions that go beyond whatever interventions may be considered necessary and recommended for their clinical care. Withdrawal from research would not, of course, involve the removal of the organ unless the organ's presence was thought to be causing harm in some way. In addition, they cannot withdraw from standard observational data that are collected routinely after any organ transplant and placed in the UNOS database.

RECOMMENDATIONS

GOAL 1: ***Improve transparency and public trust in the organ donation process for research followed by transplantation.***

RECOMMENDATION 1: The Organ Procurement and Transplantation Network, organ procurement organizations (OPOs), the Health

Resources & Services Administration, advocacy organizations, and professional associations involved in educating the general public and obtaining individual and surrogate authorization should explore, develop, and test communication strategies and materials that explain organ donor intervention research and should implement and disseminate those resources for which effective messaging has been identified. Information resources to be developed include

- **Template language to be used by all U.S. organ donor registries (e.g., departments of motor vehicles [DMVs], national registry) to ensure consistency across registries in the language used to obtain authorization for organ donation. This language should explain organ donation options in language that takes into account the wide range of degrees of health literacy among the public.**
- **Templates for DMVs, OPOs, and other entities that advocate for organ/tissue donation to use for communicating a consistent set of facts about organ donor intervention research across websites and other dissemination methods.**
- **Standardized talking points for communicating with donor surrogates and families about organ donor intervention research. These should include, at a minimum, information about donation, transplantation, and research in language that takes into account the wide range of degrees of health literacy among the public.**

GOAL 2: ***Improve the coordination and sharing of information about donor preferences.***

RECOMMENDATION 2: All active donor registries in the United States should coordinate in order to ensure a single, unified secure national donor registry that is easily accessible to organ procurement organizations. All donor registry information collected by departments of motor vehicles should automatically feed into this single national registry. Model state legislation should be developed to facilitate this merger.

GOAL 3: ***Clarify legal guidance on organ donation for the purpose of research followed by transplantation (organ donor intervention research).***

RECOMMENDATION 3: The National Conference of Commissioners on Uniform State Laws should explore revisions to the Uniform Anatomical Gift Act (UAGA) that would clarify the authorization of organ donation for the purpose of research followed by transplantation. The following possible clarifications to the UAGA should be considered:

- **When a decedent has stated a general intent to make an anatomical gift, without further specification, research followed by transplantation is permitted.**
- **Organ procurement organizations should be explicitly empowered to seek from a donor's surrogate the expansion of the authorization for an existing gift for any purpose to be used for research followed by transplantation.**

The committee also considered two options for resolving the ambiguities in the UAGA and state laws, but sensitive to trust and transparency felt this issue requires more public consultation. Therefore, the committee recommends that the Organ Procurement and Transplantation Network and transplant community should engage in public consultation and determine whether to amend the UAGA and state laws to

- **Specify that when the decedent has authorized transplantation this denotes that the gift is authorized for research followed by transplantation, or**
- **Specify research followed by transplantation as an additional purpose of donation that would be added to the list of choices for the donor.**

GOAL 4: ***Promote informed consent for transplant recipients' participation in organ donor intervention research in a manner that is compatible with the logistical complexities of organ transplantation.***

RECOMMENDATION 4: Transplant centers and organ procurement organizations, in collaboration with the Organ Procurement and Transplantation Network/United Network for Organ Sharing, professional associations, and patient advocacy organizations should develop and implement a protocol for notifying and educating potential organ transplant recipients about the possibility of being offered an organ that has been exposed to a research intervention and seeking informed consent if they agree to be part of the research study. Specifically,

- **At intake and at regular intervals thereafter, all potential recipients should be provided with information about organ donor intervention research and asked whether, at the time of organ offer, they would potentially consider accepting an organ (target organ or non-target organ) that was part of a research study. As a result of time constraints at the time of the organ offer for transplantation, only potential recipients who have previously agreed to consider**

research organs should be approached with the option to accept an available research organ.

- **At the time of being offered an organ for transplantation, each transplant candidate who will potentially receive an organ that is part of a research study—be it a target organ or a non-target organ—should be provided with information about the specific research protocol and should follow the single institutional review board's approved informed consent process for participating in that specific research study (including possible alteration or waiver of informed consent) and accepting the particular research organ offered. Given the importance of minimizing delays, information about the research protocol should be imparted through a process that ensures equitable, effective, and efficient placement and transplantation.**

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4

Research Approval, Implementation, and Oversight: Ensuring Quality and Trust

This report has examined several gaps, barriers, and opportunities in current laws, regulations, policies, and practices concerning deceased organ donor intervention research carried out as part of efforts to increase the number and improve the quality of transplantable organs. Without a central organization that can coordinate and facilitate cooperative research among a large number of institutions, this promising research is not likely to proceed at the volume, quality, and pace needed. Moreover, oversight and monitoring are needed to ensure adherence to the relevant ethical, legal, and regulatory policies and thus to promote public trust. This chapter outlines a framework for centrally administered oversight of deceased organ donor intervention research, concentrating on its essential functions.

The policy objectives that an organ donor research oversight framework should seek to achieve are to

- Ensure that scientific objectives in no way compromise the interests of deceased donors, donor families, transplant candidates or recipients, or the public. For example, interventions should always be consistent with, or seek improvements in, the care and management for donors and for transplant recipients.
- Engender the highest level of confidence from organ donors, their families, the general public, transplant candidates and recipients, donor hospitals and transplant centers. All must trust that their interests will not be compromised by research programs.
- Ensure that research activities are medically important, scientifically valid, and well conducted and that they do not compromise

the mission of donor hospitals or transplant programs. For example, studies aimed at improving transplantation for one organ should not compromise the quality of other organs that might be recovered from the same donor.
- Foster the provision of clinically useful data. Studies should be designed so that they provide information that supports critical evaluation and improvements in patient outcomes.

This chapter provides the committee's recommendations for extensive, independent, transparent, and ethics-based oversight and management of organ donor intervention research. The entire edifice of organ donation and transplantation is held together by bonds of trust among the public, prospective donors, family members of deceased donors, transplant candidates, transplant recipients, transplant centers, donor hospitals, and organ procurement organizations (OPOs), and these bonds must be retained when organ donor intervention research is implemented as a vital part of organ donation and transplantation.

CENTRALIZED MANAGEMENT OF DECEASED ORGAN DONOR INTERVENTION RESEARCH: BACKGROUND AND RATIONALE

Research has led to significant improvements in organ graft survival and transplant recipient health outcomes (Watson and Dark, 2012; Barker and Markmann, 2013). However, far less research has been conducted on improving the viability and quality of organs from deceased organ donors (organ donor intervention research). To ensure that this relatively new frontier in organ donation and transplantation research progresses in an ethical, expedited, and logistically feasible manner, centralized management and oversight are needed. Several of the unique challenges to conducting organ donor intervention research illustrate the rationale for a more centralized research system:

- *Brevity of the timeframe:* Time is extremely limited due to concerns about the viability of the organs. Finding the appropriate recipient(s) and making the most of the gift of an organ or organs involves making rapid decisions, which in turn requires clearly defined, well-vetted, and centralized processes and policies.
- *Target and non-target organs:* Because much of this research is conducted prior to the recovery of the organs from the deceased donor, the intervention may have the potential to affect not only the target organ but also the non-target organs. Recipients of non-target organs must be informed in a way that is similar to how recipients

of target organs are informed, thus adding to the complexity of the overall process (see Chapter 1).

- *Numerous and geographically dispersed stakeholders:* An organ donor managed by 1 of the 58 OPOs in the United States can provide up to eight solid organs, each of which could be transplanted by different transplant programs across the country and allocated using varied distribution schemes. Donor intervention research involving donors, donor families, OPO staff, transplant staff, and recipients (target and non-target organ) adds another layer of complexity to this already multifaceted and time-driven system.
- *Fairness:* Donated organs are a scarce and valued national resource. The critical donor organ shortage and the life-and-death nature of organ donation and transplantation require a fair and equitable system for organ allocation. Organ allocation is, for the most part, moving away from a local and regional model toward a national model. The local and regional allocation models had produced significant differences in the chances for an organ transplant candidate to receive a donor organ offer depending on where in the country the candidate lived or, in some cases, where the candidate resided in relation to his or her transplant center. Under the national model, organs can be sent across the country. A donor intervention research oversight system must ensure that any research activities that are pursued do not substantially alter the way in which organs are distributed, including the types of individuals who are eligible. Information on the research efforts must be accurately communicated with clinical stakeholders and potential recipients so as not to negatively affect potential recipients' access to organ offers.
- *Consistency:* Successful research requires consistency of performance across the multiple institutions and disparate geographic locations. Consistency will be best achieved through centralization of clinical oversight and through institutional review board (IRB) functions.
- *Efficiency:* For donor intervention research to flourish, mechanisms need to be established to coordinate and facilitate initiation and implementation of multi-center research investigations across a wide geographic area. By reducing the number of parallel and dispersed processes, a centralized oversight approach diminishes major administrative barriers to implementation, completion, and dissemination of research studies.

In 2014–2015 organ donation and transplantation professionals serving on the Donor Intervention Research Expert Panel (DIREP, see Chapter 1 for more information) concluded that an area of research as complex as

organ donor intervention research should be overseen by an independent central authority (Abt et al., 2015). As conceived by the DIREP, central oversight should serve three functions: (1) evaluating and approving proposals based on scientific merit; (2) providing ethical oversight, including the duties of an IRB, if indicated; and (3) monitoring efficacy and safety. Under this model, a central authority would act as the clearinghouse for all donor proposals and as the safety monitor for active studies. Subsequent discussions on how best to address the needs of this field led to the initiation of the National Academies of Sciences, Engineering, and Medicine study and this report. The committee preparing this report independently examined the needs and challenges in the field and came to the conclusion that central management of organ donor intervention research is necessary. The framework for that management and oversight is provided in this chapter.

FRAMEWORK FOR CENTRALIZED MANAGEMENT

Clinical research is ethically sensitive in part because patients—to whom physicians owe a duty of care—are exposed to risks and burdens to advance goals that may be external to them (namely, advancing medical knowledge for the potential benefit of future patients). As such, physician-researchers and the institutions that oversee them maintain divided loyalties. Policies established to protect human subjects have sought to resolve this moral tension by requiring that human research studies undergo prospective and independent ethical review by committees (in the United States, these committees are IRBs). The stipulations governing IRB membership require a board to include, in addition to subject matter experts, lay individuals who represent a broad spectrum of interested constituents. U.S. federal regulations specify criteria that IRBs should apply to the ethical review of research protocols (see Chapter 3). The National Academies committee sought to develop an approach for centralized management of donor intervention research that would incorporate these key features of an ethics-based review of research protocols.

Organ donor intervention research involves three different parties as participants in the research—donors, target organ recipients, and non-target organ recipients—with each deserving specific considerations, all of which are needed to ensure that a respectful, fair, and trustworthy donation and transplantation system is in place in the United States. For deceased organ donors, their families, and their surrogate decision makers, the focus is on fulfilling these people's decisions regarding organ donation and honoring their gift of life for other individuals. For both target organ recipients and non-target organ recipients, the protections necessitate exploring and implementing appropriate informed consent processes for research participants as determined by the IRB.

The committee considered the structure for oversight of organ donor intervention research and recommends that the framework should consist of three affiliated entities:

- a centrally administered and standing Donor-Research Oversight Committee (D-ROC),
- a single IRB for donor intervention research, and
- data safety monitoring boards (DSMBs).

The goals and responsibilities of each of these are described in detail below. The committee recognizes that other models could be developed for oversight; however, it believes that the functions it describes should be considered key elements of whichever model is used. Organizational relationships between D-ROC, the single IRB, and the DSMBs should be constructed such that these entities work independently but cooperatively.

DONOR RESEARCH OVERSIGHT COMMITTEE

The committee envisions D-ROC as a centrally administered standing committee. As part of its charter, D-ROC should be empowered to work with stakeholders to prioritize, review, implement, and track research protocols as well as to develop and disseminate information about organ donor intervention research. D-ROC should be a newly formed entity chartered to coordinate and oversee donor intervention research. Having such an oversight body will require adequate staff and appropriate expertise in governance, information technology, transplant medicine and surgery, organ donation and procurement, ethics, and law as well as public representation. Discussions below highlight organizational and funding issues.

Context

A centrally administered committee or board responsible for coordinating complex research protocols across institutional and geographic boundaries is not without precedent. As noted in Box 4-1, the Clinical Trials Working Group (CTWG) helped restructure the National Cancer Institute (NCI)-supported national clinical trials enterprise devoted to using molecular medicine to advance oncologic clinical practice (NCI, 2005). The NRG Oncology Foundation administers a national program that conducts "practice-changing" multi-institutional clinical and translational research on gynecologic, breast, and prostate cancers. Another example comes from the United Kingdom, where the Research, Innovation and Novel Technologies Advisory Group (RINTAG) supports innovation and research expected to lead to improved rates of organ donation or improved organ function

Box 4-1 EXAMPLES OF RESEARCH OVERSIGHT AND COLLABORATIVE ORGANIZATIONS

RINTAG (Research, Innovation and Novel Technologies Advisory Group) of the National Health System Blood and Transplant (NHSBT) organization: RINTAG is a United Kingdom–based advisory group that works closely with NHSBT and other stakeholders to provide support and oversight for innovation, research, and implementation of novel technologies and developments, with the goal of improving the rates of solid organ donation, organ function, and recipient health outcomes. The advisory group is composed of members from solid organ advisory groups, NHSBT, the Organ Donation and Transplantation Directorate, and various research partnerships. RINTAG has the following aims and roles:

- Advise stakeholders of new and ongoing research and innovations that may have an impact on the donation and transplantation pathway.
- Formally assess proposed methodologies for all research projects submitted to NHSBT for support to certify that appropriate approvals have been received from all relevant stakeholders and to ensure that the proposed research activities will not disrupt the operation or perception of donation and transplantation services.
- Review the progress of NHSBT-supported projects and establish and maintain a project registry.
- Coordinate access to organs for approved research purposes and review the current allocation of organs and tissues for research by NHSBT.
- Develop frameworks for the introduction of technologies and developments into clinical practice (NHS Blood and Transplant, 2017).

NRG Oncology: Established in 2014, NRG Oncology is a nonprofit research organization within the National Cancer Institute's (NCI's) National Clinical Trials Network that conducts multi-institutional clinical research to inform practice and policy. The collaborative organization was formed by the joining of the National Surgical Adjuvant Breast and Bowel Project, the Radiation Therapy Oncology Group, and the

and better outcomes for organ transplant recipients (NHS Blood and Transplant, 2017).

With regard to the steps necessary to create a cohesive national research system to carry out well-conducted clinical trials, CTWG identified four initial critical goals (NCI, 2005). The committee adapted these goals for a system for D-ROC's support of donor intervention research as follows:

- *Ensure coordination and cooperation among the functionally diverse components:* All members of the organ donation and transplantation community should be represented, including community members, donor families, transplant recipients, OPOs, transplant centers, donor hospitals, federal regulatory agencies, and industry.

Gynecologic Oncology Group and is composed of tiered committees, centers, and boards that are responsible for carrying out the mission of the organization. The centralized NRG Oncology board of directors is responsible for the allocation of resources to committees, which are required to submit all reports and recommendations for the approval of the board (NRG Oncology, 2017; RTOG Foundation, 2017).

Clinical Trials Working Group (CTWG): CTWG was established to advise the National Cancer Advisory Board on the restructuring of NCI-supported national clinical trials enterprise to more effectively and efficiently grow the impact of their work. The working group is composed of individuals from academia, pharmaceuticals and biotechnology, patient advocacy groups, oncology practices, and government institutions such as the U.S. Food and Drug Administration, Centers for Medicare & Medicaid Services, and NCI. CTWG identified the following four key components for an improved, evidence-based clinical trials enterprise structure:

1. "Improve coordination and cooperation among the functionally diverse components of the current system, including industry and federal regulatory agencies."
2. "Improve prioritization and scientific quality by developing an open and transparent process for the design and prioritization of clinical trials that are science-driven and meet the needs of patient care."
3. "Improve standardization of tools and procedures for trial design, data capture, data sharing, and administrative functions to minimize duplication of effort, and to facilitate development of a shared infrastructure to support an integrated national cancer clinical trials network."
4. "Improve operational efficiency by increasing the rate of patient accrual and reducing operational barriers so that trials can be initiated and executed in a timely, cost-effective manner" (NCI, 2005, p. 2).

- *Establish mechanisms to prioritize and monitor clinical studies:* Create a standard and transparent process to prioritize proposals based on scientific quality, clinical need, and donor availability and to monitor active protocols for efficacy and safety, with reassessments of priorities as needed as the studies unfold.
- *Standardize tools and procedures:* Standard processes should be developed to ensure fairness and minimize conflict among stakeholders, to promote effective trial design that will lead to valid new knowledge, to maintain consistency across diverse geography and across the range of organ donation and transplant professionals and organizations involved in this research, to maximize data capture and opportunities for data sharing, to minimize duplication

of effort, and to facilitate the progressive development of a donor intervention research clinical trials network.

- *Reduce operational barriers:* Strive for operational efficiencies that reduce time to implementation, maximize study participant accrual, catalog ongoing research efforts, and minimize costs without sacrificing safety.

D-ROC Core Competencies and Responsibilities

The committee envisions D-ROC as a centralized organization that would provide oversight to organ donor intervention research and would link with a single IRB devoted to these studies and with the DSMB working with each study to facilitate research and research dissemination. D-ROC would have responsibilities for overseeing the integration of deceased organ donor intervention research nationally to achieve the goals outlined in this report. D-ROC's core responsibilities are highlighted in Box 4-2. The core competencies necessary to meet these responsibilities would include transplantation clinical care and research, transplant epidemiology, governance, law, ethics, relevant scientific and medical disciplines, project management and conflict resolution, communications, information technology, and data analysis. An essential part of this responsibility would be to ensure that relevant stakeholders from the donor and recipient communities are involved and that research results are widely and appropriately disseminated. An envisioned "life-cycle" for a donor intervention research proposal and the roles for the D-ROC in the process are described later in this chapter.

Review and Prioritize Donor Intervention Proposals

One of the major responsibilities of D-ROC would be to perform the initial review of all proposals for organ donor intervention research for

Box 4-2 CORE RESPONSIBILITIES OF THE DONOR RESEARCH OVERSIGHT COMMITTEE

- Review and prioritize donor intervention proposals
- Assess and monitor the impact of organ donor intervention research on organ allocation and distribution
- Coordinate and facilitate clinical and research informatics and promote communications
- Promote effective trial design
- Maintain liaisons with key external groups

their scientific merit and clinical impact. D-ROC should establish a core set of policies that set conditions for the submission of protocols to the research oversight system. Conditions should include commitments to

- disclosing potential conflicts of interest;
- systematic review of evidence supporting each trial;
- prospective trial registration;
- active dissemination of results, including publication in the peer-reviewed literature;
- reporting of results according to contemporary standards; and
- dissemination of data, according to data-sharing and privacy standards.

One of the key assessments that will need to be made by clinical and research teams, in conjunction with the IRB, is whether their activity qualifies as a research study or as a quality improvement (QI) effort, with the latter being a local activity that is not within the purview of D-ROC oversight. As discussed in Chapter 1, there is an ongoing discussion about the boundaries between quality improvement and research in this field, as is the case in many areas of medicine (Casarett et al., 2000; Baily et al., 2006). Given this situation, the committee urges that D-ROC and the single IRB establish clear criteria—including paradigmatic cases of QI and research—that transplantation teams might use in deciding whether their activities would fall under D-ROC's purview and also make clear the implications of any decisions based on those criteria, particularly implications regarding patient consent and oversight mechanisms. Many surgical procedures, including those in transplantation, have emerged through an iterative and incremental series of cases, a process that in some cases leans toward QI. However, the boundaries between QI and research depend on many factors, including the nature and extent of the process changes, the way that interventions are conducted, and the nature of patient outcomes follow-up. The criteria developed by D-ROC to differentiate QI and research in organ donor intervention studies and the mechanisms that D-ROC uses to implement and enforce those criteria will need to place utmost emphasis on ensuring the safety of transplant recipients (target organ recipients and non-target organ recipients) and upholding the public's trust and confidence throughout the organ donation and transplantation process.

An early goal of D-ROC should be the development of a standard tool that D-ROC and the research, clinical, and transplant communities can use to differentiate QI and research and determine the need for IRB approval. For example, the Research Institute of the Children's Hospital of Philadelphia developed a set of questions and a worksheet on this issue based in part on work by the Hastings Center (Baily et al., 2006; CHOP

Research Institute, 2015; see Table 4-1). The criteria offered by Casarett and colleagues (2000) are also helpful. A concern of the committee is that investigators may use QI as a mechanism for avoiding the more time- and resource-intensive efforts required to adhere to human research protections. Therefore, the committee urges that careful attention be paid to the development of criteria delineating these two distinct pathways for donor inter-

TABLE 4-1
Quality Improvement or Research Worksheet

	Issue and Guidance	Rating	
1	Are patients randomized into different intervention groups in order to enhance confidence in differences that might be obscured by nonrandom selection? *Randomization done to achieve equitable allocation of a scarce resource need not be considered and would not result in a yes here.*	☐ yes	☐ no
2	Does the project seek to test issues that are beyond current science and experience such as new treatments (i.e., is there much controversy about whether the intervention will be beneficial to actual patients, or is it designed simply to move existing evidence into practice?). *If the project is performed to implement existing knowledge to improve care—rather than to develop new knowledge—answer "no."*	☐ yes	☐ no
3	Are researchers who have no ongoing commitment to improvement of the local care situation (and who may well have conflicts of interest with the patients involved) involved in key project roles? *Generally answer "yes" even if others on the team do have professional commitments. However, where the project leaders with no clinical commitment are unaffiliated with the project site, it may be that the project site is not engaged—and does not require IRB approval/oversight—even if the project leaders' roles do require IRB oversight at their institutions.*	☐ yes	☐ no
4	Is the protocol fixed with a fixed goal, methodology, population, and time period? *If frequent adjustments are made in the intervention, the measurement, and even the goal over time as experience accumulates, the answer is more likely "no."*	☐ yes	☐ no
5	Will there be delayed or ineffective feedback of data from monitoring the implementation of changes? *Answer "yes" especially if feedback is delayed or altered in order to avoid biasing the interpretation of data.*	☐ yes	☐ no
6	Is the project funded by an outside organization with a commercial interest in the use of the results? Is the sponsor a manufacturer with an interest in the outcome of the project relevant to its products? Is it a nonprofit foundation that typically funds research, or internal research accounts? *If the project is funded by third-party payers through clinical reimbursement incentives, or through internal clinical/operations funds vs. research funds, the answer to this question is more likely to be "no."*	☐ yes	☐ no

NOTES: If the weight of the answers tends toward "yes" overall, the project should be considered "research" and approved by an IRB prior to implementation. If the weight of the answers tends toward "no," the project is not "research" and is not subject to IRB oversight unless local institutional policies differ. Answering "yes" to sequence #1 or #2—even if all other answers are "no"—typically will result in a finding that the project constitutes research. *It is important to consult with your local IRB if you are unsure how they would handle a particular case, as the analysis of the above issues cannot always be entirely objective and IRB policies and approaches vary significantly.*

SOURCE: CHOP Research Institute, 2015. Reprinted with permission from Rachel Nosowsky, Esq.

vention studies so that the option to conduct QI studies is not abused. For example, D-ROC could randomly audit QI activities to examine whether donation and transplantation centers are using QI appropriately. Both QI and research efforts will play a critical role in advancing the field.

Because of the scarcity of organs available for transplantation and the potential for many donor intervention research studies occurring at the same time, D-ROC will need to determine priority among the research studies. As discussed by Gelinas and colleagues (2017), when a pool of patients is limited, clinical trials for the relevant patient population will end up competing for participants, with the competition likely resulting in low patient accrual and recruitment shortfalls for the individual studies. An early priority of D-ROC could be to develop the criteria by which it will assess and prioritize new protocols for donor intervention research. Criteria will be needed in order to limit the negative effects of competition on the ability of researchers to recruit and successfully enroll donor organs and transplant candidates in studies. The review by D-ROC would assign an impact/priority score to each proposed protocol based on variables that would include but not be limited to

- scientific strength;
- the balance between risks and probable benefits (with input from the single IRB; see description of the responsibilities of the IRB);
- the potential to increase the number and quality of donated organs for transplantation and the potential to improve graft and patient outcomes;
- fairness and justice, including fairness in subject selection and the potential to improve outcomes for underserved populations;
- inclusion and exclusion criteria of the proposed research;
- any impact on ongoing or planned studies; and
- the innovative quality of the proposed study.

Based on these priority factors, D-ROC would make its decisions regarding the approval and implementation of the study and would work with the IRB to ensure that the risk level and other information on the research would be communicated in an expedited manner to allow for informed decisions by the transplant team and the potential recipients. D-ROC would have responsibilities to ensure that its processes and policies adhere to the strictest ethical standards and also to facilitate the optimal allocation of organs that are involved in research.

Assess and Monitor the Impact of Organ Donor Intervention Research on Organ Allocation

Some organ donor intervention research could have the potential to have negative impacts on waitlist transplant candidates by distorting the organ allocation system. Beyond evaluating the balance of risks and benefits to participants in a specific study (a task for both the D-ROC and the single IRB), it will also be important to consider a study's potential impact on the allocation of organs within the national system and on the morbidity and mortality of waitlist transplant candidates as well as its possible effects on transplant outcomes for all organs, including non-target organs, that are exposed to the research intervention.

Donor intervention research protocols could threaten fairness and equity in organ distribution in a variety of ways, as suggested by the following examples. First, a study could restrict the allocation of research organs to a subset of transplant candidates because of protocol inclusion and exclusion criteria. Such an attempt to advance knowledge of how to treat this subset of transplant candidates and future patients might mean that organs are directed preferentially to candidates based on their protocol eligibility rather than priority on the wait list. It is important to avoid this kind of restriction in a study design. Second, transplant candidates who decline a research organ may wait longer for a transplant and, in the process, may become sicker and even die before receiving another organ offer. As a result, some transplant candidates or transplant teams may feel pressure to accept research organs. Third, donor intervention research targeted at a particular organ may have an impact on non-target organs. Even if it is unlikely, for example, that a specific intervention targeting kidneys will have a negative impact on the efficacy or safety of heart transplantations, this cannot be ruled out in advance and thus raises a concern about fairness and equity in the organ allocation processes.

D-ROC should assess research protocols to determine whether they have possible negative impacts on donor organs or recipients. To this end, D-ROC could require researchers to provide an impact statement that indicates the likelihood, severity, and distribution of possible adverse impacts and how they can be avoided or mitigated. Where possible, D-ROC should require changes in studies that are designed so as to minimize adverse impacts and reduce inequitable distribution, and it should assign priority to studies with little likelihood of serious adverse effects.

Because it is difficult to predict such adverse effects with precision, systematic monitoring should be the responsibility of D-ROC. Accordingly, D-ROC should develop a comprehensive monitoring plan. This plan goes beyond the monitoring undertaken by the single DSMB, which focuses on participants in the research trial. This broader monitoring, by contrast,

would focus on a complex set of possible impacts on parties outside of those directly participating in the research trial. For example, if monitoring reveals that some donor intervention research has a negative impact on transplant candidates on the waiting list for a particular target organ or on recipients of non-target organs, the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) will need to determine the appropriate course of action to ensure the fair distribution of organs donated for transplantation. Robust and dynamic tools such as dashboard technology should be employed to manage this complex process.

Coordinate and Facilitate Clinical and Research Informatics and Promote Communications

A primary role for D-ROC will be ensuring that the necessary informatics and communications infrastructure is in place and actively implemented to facilitate and promote organ donor intervention research. The goals of data sharing include facilitating discovery science while avoiding duplication and ensuring reproducibility; increasing the understanding of human disease; improving the design, efficiency, and quality of clinical trials; and managing the cost and administrative burden of clinical research (IOM, 2015). All of these goals are consistent with the aims of a national program in organ donor intervention research. The Institute of Medicine report on responsible data sharing (2015) made four recommendations that could be applied to thinking about data sharing for the organ donation and transplantation communities:

- Principals in clinical trials should create and foster a culture of sharing the trial data as standard operating procedure and should "commit to responsible strategies aimed at maximizing the benefits, minimizing the risks, and overcoming the challenges of sharing clinical trial data for all parties" (p. 4).
- Both the investigators and sponsors of clinical trials should share the various types of trial information and data as appropriate.
- Researchers should use data agreements and create independent review panels for trial data stewardship.
- Issues related to database infrastructure, technology, workforce, and sustainability need to be addressed.

Online registry of organ donor intervention studies A single online registry of organ donor intervention studies is needed to catalog these research studies with the goal of providing access to non-proprietary study information. The registry should be a dynamic tool that can be used by the D-ROC, donation service areas, investigators, and clinicians to anticipate resource

use, set budgets, and track research activity across the organ transplantation field. Additionally, the registry could provide information to the general public on the studies. The registry database could be implemented using an existing platform such as www.ClinicalTrials.gov. The registry should be readily accessible to transplant candidates, health care providers, and the interested public (including prospective donors).

Examples of registry data to be included are study status (e.g., active studies, completed studies, studies in queue, studies under review, studies requested to address specific areas of interest), basic study design elements (e.g., projected start and close date, sample size, arms, eligibility), and links to contact information. Ideally, the registry would be a useful tool for the prioritization of new proposals—for example, as an aid to identify studies that might compete or place stress on overlapping resources.

Data management tools and data sharing Coordinated data management tools will also be critical to the success of organ donor intervention research in several ways. First, in order to track the outcomes of this research, investigators will need to be able to identify the research organ in UNet[SM][1] and other relevant databases, including the Scientific Registry of Transplant Recipients (SRTR) database that brings together multiple data sources, so that outcomes of recipients of research organs can be followed and analyzed (SRTR, 2017). Data fields will need to be added to allow for the designation of the organ as a research organ, to note other relevant information about the research, and to link to the research protocol so that potential recipients can be informed about the research protocol and research outcomes can be identified and tracked. D-ROC should lead this effort in collaboration with OPTN/UNOS, OPOs, professional associations, and other stakeholders.

Second, information on the research studies will need to be shared with transplant center clinicians and with potential organ recipients to enable decisions regarding offers of research organs (see Chapter 3). This information could be provided through current mechanisms for sharing information about clinical transplant decisions (e.g., UNet[SM]) or through other mechanisms determined to be efficient and fair.

Additionally, other data-sharing tools and approaches could be used to facilitate organ donor intervention research. One possibility is increasing the sharing of donor management data to enable the development of innovative or novel donor management strategies. Data sharing between

[1] UNet[SM] is an online database system with the OPTN/UNOS data (October 1, 1987, and forward) on every organ donation and transplant event in the United States (UNOS, 2017). UNet[SM] has a variety of modules that are used to register transplant candidates for the waiting list, conduct organ matching, and store data on transplant candidates, organ donors, and transplant recipients (UNOS, 2017).

OPOs and also between OPOs and transplant programs that is coordinated or overseen by D-ROC has the potential to address this need. OPOs collect data prospectively and in real time, beginning as soon as the OPO is notified of a potential donor and continuing through the post-transplant time period for those potential donors who become actual donors. In addition to collecting mandated data such as demographics, history, and organ function, OPOs collect information on vital signs, medications administered and dose adjustments, fluid levels, test results of all kinds, and any interventions that are administered. Although OPOs collect these data, the data generally remain isolated and are used primarily to inform local practice or for documentation should questions arise about a particular transplantation. The combined data of all OPOs would be a powerful source with which to guide innovation and support the development of novel strategies for organ donor intervention research. Thus, another focus for D-ROC's informatics could be to develop a pan-OPO donor management database that connects with existing relevant data sources.

Promote scientific and public communications D-ROC's website, as well as other information technology and communications resources, should be developed and maintained with a focus on ensuring that research results are disseminated broadly to the transplant community, to the broader research community, and to the general public. As noted in Chapter 3, messaging and communications on donor intervention research need to meet the health literacy needs across the general public. After a trial is completed, the results should be shared with the organ donation and transplantation community, the broader scientific community, and the public through standard mechanisms (e.g., presentations, articles) as well as innovative research dissemination mechanisms. Not just "positive" results but also inconclusive and negative results need to be published and presented. In this context negative and inconclusive results are as important as positive results for preventing the repetition of disproven hypotheses. Outcomes, learnings, and safety alerts could be disseminated through multiple avenues of communication.

To assure the rapid communication of findings and to avoid conflicts between stakeholders, D-ROC should establish rules of conduct for investigators for publication, presentations, publicity, intellectual property, data access, non-disclosure agreements, relationships with industry sponsors, and personal rights and responsibilities. Additionally, D-ROC should produce an annual public report of all its professional and operational activities. This could include summaries and references for concluded, active, and pending studies.

Promote Effective Trial Design

One challenge in deceased organ donor intervention research is that the most accurate and precise method of determining outcomes and significance—the large, multicenter, randomized controlled clinical trial—is very difficult to perform in this context. There are opportunities to explore other research designs for these studies, as is being done in other areas of clinical research (Chow and Chang, 2008; Califf et al., 2012; Lauer and D'Agostino, 2013). D-ROC should facilitate the exploration of appropriate and innovative and effective research designs for the questions to which it seeks answers. Ensuring the validity of research using innovative approaches can be a responsibility of the D-ROC and could help solidify public trust (IOM, 2013a,b). These efforts can also assist in determining the quality and strength of the evidence that research generates, which is essential to developing standards of care (see the discussion of the principle of validity in Chapter 2).

Maintain Liaisons with Key External Groups

To help maintain the alignment of all stakeholders and facilitate organ donor intervention research, D-ROC should establish formal working relationships with key external agencies and organizations—for example, with the Centers for Medicare & Medicaid Services (CMS). In this case, the common goal would be to ensure that the CMS conditions of participation (defined below) are constructed to encourage and not penalize organizations that participate in organ donor intervention research.

Conditions of participation are policies and regulations designated by CMS to identify and maintain high-quality effective donation and transplantation programs (see Box 4-3). Transplant centers, OPOs, and donor hospitals must meet conditions of participation standards in order to be eligible to participate in and receive reimbursement through Medicare and Medicaid. The sustainability of these programs is thus tied to meeting these performance and outcome measures. When an institution considers participating in a donor intervention research study, the potential for the study to affect the institution's outcomes relevant to the conditions of participation may be a major factor in its decision whether to participate. CMS has made some changes to its criteria that are intended to address these issues (see Box 4-3). D-ROC could work with CMS to create conditions of participation incentives that foster positive attitudes toward donor intervention research and align with those of the organ donation and transplant community.

Box 4-3 CENTERS FOR MEDICARE & MEDICAID SERVICES (CMS) REGULATIONS RELEVANT TO CONDITIONS OF PARTICIPATION AND ORGAN DONOR INTERVENTION RESEARCH

2014: The revised CMS regulations on conditions of participation clarified the mitigating-factors process for the assessment of outcomes of solid organ transplant programs and noted that innovative transplantation practices supported by evidence-based research would be considered an acceptable mitigating factor in evaluating program performance (42 C.F.R. § 488.61).

2016: In May 2016, CMS issued revised guidelines for outcome thresholds for solid organ transplant programs. The revisions expanded the targeted outcome threshold to 185 percent of the risk-adjusted national average for 1-year post-transplant outcomes. The policy change noted that "1-year post-transplant outcomes have improved for all organ types since 2007, when the CMS solid organ transplant regulation was first implemented and that . . . because individual programs are compared against the risk-adjusted national average, the national improvement had made the CMS outcomes standard increasingly stringent and made it more difficult for individual transplant programs to maintain compliance with the outcomes standards" (CMS, 2016a).

2016: In December 2016, CMS noted a modification to its criteria relevant to determining non-compliance with transplant program outcome requirements (CMS, 2016b).

SINGLE IRB FOR ORGAN DONOR INTERVENTION RESEARCH

Because organ donor intervention research will likely involve coordination across multiple OPOs, donor hospitals, and transplant centers, it will be necessary to obtain consent from recipients across many sites in a very short period of time and to have all potential sites on board with the centralized processes. This is particularly important for donor hospitals, which may only occasionally be involved in the organ donation process and may not be familiar with organ donor intervention research.

The standard model of IRB oversight for multi-site studies, in which each research institution has to review and approve the research protocol, is poorly suited to the context in which organ donor intervention studies take place. Local IRB oversight—with the challenges of inconsistent amendment requirements and the near-certain guarantee of these studies being conducted across many transplant centers—would likely severely limit the feasibility of donor intervention research. Taking these two things together, the committee concluded that a single IRB for all of organ donor intervention research is necessary to ensure adequate human subjects protections under the conditions in which this research will be performed. The single

IRB would make the decisions regarding informed consent for research for recipients of both target and non-target organs (discussed in depth in Chapter 3). The single IRB could be an independent central IRB or another alternative is to designate a current IRB to be the IRB of record with all institutions signing a letter of agreement (e.g., see smartirb.org).

A single IRB would offer the advantages of developing and maintaining core expertise in organ donor intervention research. The IRB would oversee human research protections and ensure that processes are followed in accord with the relevant regulatory and policy requirements and guidance, particularly the federal Common Rule for human research protections.[2]

Box 4-4 summarizes the recent determination by the National Institutes of Health (NIH) that single IRBs are preferred for multisite research because they decrease the burden of redundant reviews by creating one platform for protocol analysis and oversight. Furthermore, the final rule for federal policy on human subjects protections stipulates the use of a single IRB for multi-institutional trials; while most provisions of the Final Rule take effect in January 2018, this requirement will not take effect until January 2020 (*Federal Register*, 2017). The Final Rule for human subjects protections also "removes the requirement to conduct continuing review of ongoing research for studies that undergo expedited review and for studies that have completed study interventions and are merely analyzing study data or involve only observational follow-up in conjunction with standard clinical care" (*Federal Register*, 2017).

Examples of single IRBs include those used by NeuroNext and NCI (Marsolo, 2012; Mascette et al., 2012; Check et al., 2013; Flynn et al., 2013) (see Box 4-5). Multicenter trials using a single IRB have the potential to accelerate enrollment and subject accrual since timeframes for the approval process vary widely between local IRBs. The single IRB can be an effective, convenient, and efficient method of addressing the need for an IRB operating in a complex environment.

The single IRB has the mandate to determine that "risks to subjects are reasonable in relation to anticipated benefits."[3] One of its responsibilities would be to conduct a prospective risk–benefit assessment of each research protocol that is based on the systematic appraisal conducted by the investigators of the balance of risks (probability and magnitude of harms) to transplant recipients and the probable benefits to recipients and to future transplant candidates (see the discussion of beneficence/utility in Chapter 2). This would include determining the potential risk and impact of the research protocol on both the target organ(s) and non-target organs. As discussed in Chapter 3, the committee suggests that studies be categorized into three

[2] 45 C.F.R. Part 46.
[3] 45 C.F.R. § 46.111.

Box 4-4 FEDERAL POLICIES AND REGULATIONS

Final NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research

"The National Institutes of Health (NIH) is issuing this policy on the use of a single Institutional Review Board (IRB) for multi-site research to establish the expectation that a single IRB (sIRB) of record will be used in the ethical review of non-exempt human subjects research protocols funded by the NIH that are carried out at more than one site in the United States. The goal of this policy is to enhance and streamline the IRB review process in the context of multi-site research so that research can proceed as effectively and expeditiously as possible. Eliminating duplicative IRB review is expected to reduce unnecessary administrative burdens and systemic inefficiencies without diminishing human subjects protections. The shift in workload away from conducting redundant reviews is also expected to allow IRBs to concentrate more time and attention on the review of single site protocols, thereby enhancing research oversight" (NIH, 2016).

Final Rule—Federal Policy for the Protection of Human Subjects

"Creates a requirement for U.S.-based institutions engaged in cooperative research to use a single IRB for that portion of the research that takes place within the United States, with certain exceptions. This requirement becomes effective 3 years after publication of the final rule" (*Federal Register*, 2017).

Box 4-5 EXAMPLES OF THE USE OF SINGLE CENTRAL INSTITUTIONAL REVIEW BOARDS

NCI Central IRB Initiative—Efforts to improve the effectiveness and efficiency of trials for new cancer-related therapeutics and technologies led to the establishment of NCI's Central IRB (CIRB) Initiative. The centralized structure of the NCI CIRB Initiative allows for the use of a single protocol across multiple study sites, which reduces burdens on local IRBs, allows for rapid enrollment of patients by local investigators, and establishes a high level protection for the participants of NCI trials. Currently there are four CIRBs focused on specific aspects of adult and pediatric cancer clinical trials. In this independent model, the CIRB is the sole IRB of record and is responsible for study review as well as the review of considerations regarding the local context for enrolled institutions (NCI, 2016; CIRB, 2017).

NeuroNEXT—This initiative of the National Institute of Neurological Disorders and Stroke (NINDS) is focused on conducting exploratory trials on the next generation of neurologic treatments. Research proposals from industry, academic institutions, and foundations are evaluated by NINDS for mission relevance and institute priority and by the NeuroNEXT Executive Committee for network feasibility. Protocol working groups develop the grant applications, which are then submitted for scientific review. The initiative includes a clinical coordinating center and a data coordinating center. The network uses a master clinical trial agreement and a central IRB (NeuroNEXT, 2017a,b).

levels: 1+ (no more than minimal risk), 2+ (slightly greater than minimal risk), and 3+ (significant risk). The IRB's assessment of the risk level would be conveyed to D-ROC as part of the input into D-ROC's prioritization of the study. The designated risk level would be used to develop the informed consent plan. Part of the informed consent plan would also include the delineation of data collection efforts relevant to human subjects for the research study as determined by the investigators working with the single IRB and the DSMB.

The Common Rule sets some minimum requirements for IRB composition and delineates the IRB's responsibility in the review of research.[4] IRBs are required to include at least five members with "varying backgrounds to promote complete and adequate review of research activities." IRBs shall also be

> sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.[5]

For the single IRB on organ donor intervention research, expertise would be needed in organ donation and transplantation, relevant medical and scientific disciplines, ethics, and law, and it would require members who bring both donor and recipient perspectives to the board.

DSMBs

DSMBs are independent committees that oversee the conduct of clinical trials. They serve several broad purposes. First, they are charged with reviewing incoming study data in order to assure that the risk–benefit ratio of an ongoing trial has not shifted. DSMBs can advise study sponsors to discontinue or amend the design of a study under certain conditions. For example, the DSMB could determine, on the basis of the incoming study data, that the investigation has become unsafe for participants and thus should be terminated early. Or it could determine that efficacy has been established before the study was scheduled to end. Moreover, severe protocol deviations or seriously flagging recruitment could indicate that the research will probably not produce valid results and that its probable benefits no longer outweigh its risks to participants. Second, DSMBs can advise on and evaluate protocol amendments. For example, if recruitment becomes

[4] 45 C.F.R. 46 § 107 and 45 C.F.R. 46 § 109.
[5] 45 C.F.R. 46 § 107.

a concern, DSMBs can advise on broadening eligibility criteria in order to access a wider population. Third, DSMBs can evaluate whether patients need to be informed of new developments in a trial. In contrast with IRBs, there are fewer regulatory or legal standards for DSMB oversight. DSMBs typically have a charter that stipulates roles and responsibilities.

The DSMB for a research study establishes study-stopping criteria based on outcomes for target and non-target organ recipients. The DSMB would need to interface with the investigators before study initiation to ensure that outcomes necessary for monitoring target organs and non-target organs (and the recipients those organs have been transplanted into) are built into the protocol as needed. Safety concerns should be brought directly to the DSMB while other issues, such as opportunities to improve efficiency or to make operational changes based on observations in the field, may be acted on by mechanisms established by D-ROC.

The DSMBs for organ donor intervention research could be organized around a single research study or a set of studies. The key as described below will be for D-ROC to have the administrative capacity to establish DSMBs as they are needed.

STRUCTURE AND OPERATIONS FOR CENTRALIZED MANAGEMENT OF ORGAN DONOR INTERVENTION RESEARCH

The centralized management of organ donor intervention research will require the involvement and commitment of the organ donation and transplantation community. The committee explored several options for the management structure that could best get this endeavor off the ground and running.

One option would be for D-ROC to be a collaborative effort managed by multiple agencies and organizations. Although the full range of expertise of the donation and transplantation community is needed for any endeavor of this nature to succeed, the committee believes that there is value in having a more centralized approach to the management of this research effort. A second option would be to form a non-profit research organization. NRG Oncology provides an example of a successful approach (NRG Oncology, 2017). The committee sees value in this option but at this point in the evolution of organ donor intervention research there may not yet be the base of funding support to make this option viable. It is one option that could be strongly considered at some point in the future.

A third option would be to organize D-ROC under the auspices of OPTN. OPTN provides the long-term ongoing organizational structure that through the Health Resources & Services Administration's (HRSA's) support sets policies and implements allocation, data collection, and many other efforts that enable organ donation and transplantation to be carried

out effectively. The development of OPTN policies includes public participation and comment and this would be valuable in the initiation of D-ROC and in the working out of the details of D-ROC's structure and operations. Organizationally, OPTN/UNOS could add the staffing needed to implement D-ROC and could draw on and supplement its robust voluntary network of experts to find the appropriate technical, clinical, governance, regulatory, legal, and public awareness expertise needed. Additionally, donor families and transplant recipients are integral to the work of OPTN/UNOS and would be vital to D-ROC's efforts. D-ROC could also draw on OPTN/UNOS staffing and volunteer expertise to develop and sustain the DSMB capabilities needed.

The committee emphasizes the urgent need to implement the centralized management of organ donor intervention research in order to facilitate this research that is critically needed to improve the quantity and quality of organs for transplantation. Implementation of D-ROC could be done in phases with OPTN and the donation and transplant community establishing a charter, initial funding, rules for governance, administrative policies and a framework that should include a single IRB, the integration of DSMBs for the specific studies, and a plan for project and data management and communications. After the initial framework is established, D-ROC could evolve into a more complex organization.

The committee believes that it is critical to the success of organ donor intervention research that all donor intervention research studies should be reviewed by a single IRB that has the appropriate scientific, ethical and regulatory expertise. As previously discussed, the committee recognizes that the IRB function could be done by (1) creating an independent central IRB or (2) contracting with an existing IRB that has appropriate scientific, ethical and regulatory expertise. The single IRB for organ donor intervention research may be a free-standing (central) IRB or part of an academic medical center willing to serve as the IRB of record for the multiple sites. The committee believes that D-ROC should have flexibility in determining how to best constitute or contract out the single IRB's functions.

Organizational working relationships among D-ROC, the single IRB, and the DSMBs will need to be constructed so that independence is achieved but with close communication, in part through the data sharing mechanisms outlined above.

Setting up the organizational framework in the manner described above will provide the opportunities for funding from multiple sources. Research investigators will be funded by the usual mechanisms for biomedical research (primarily government, industry, foundation, and institutional support). In addition to the potential for HRSA and other government agency funding sources, further funds for D-ROC could include fees and income from research opportunities (e.g., industry partnerships, process improvement consultation, donations). Funding for the single IRB and for the work

of the DSMBs could come from member fees, fees for application review, and consultation services.

TIMELINE AND INTEGRATED PROCESS

The research process envisioned by the committee would consist of three stages: (1) submission and approval of research protocols; (2) planning, implementation, and monitoring; and (3) the analysis and dissemination of results and archiving in a retrievable catalog. D-ROC, the single IRB, and the DSMB for the specific study would work together to oversee the implementation and dissemination of donor intervention research, which is critically needed to improve the lives of individuals through improving the quality and quantity of donated organs.

Stage 1: Submission and Approval

Research proposals would be submitted to D-ROC. An initial review by the D-ROC would assign an impact/priority score to the proposed protocol based on the variables described earlier in the chapter. The IRB would provide input to D-ROC on the risk level. Any issues identified by the IRB would be negotiated with the study sponsor and researchers. Proposals would not move forward until approved by the single IRB and D-ROC.

If approved for implementation, a protocol would be submitted to the study's DSMB. The DSMB and the study sponsor would directly negotiate stopping rules, monitoring practices, and other criteria deemed appropriate for the conduct of the proposed study. Upon approval and before initiation, the research protocol would be registered in the public database as discussed above. Sponsors would determine whether and when to interact with the U.S. Food and Drug Administration.

Stage 2: Planning, Implementation, and Monitoring

After approval by the IRB and the study's DSMB, D-ROC would work with researchers to develop a management plan, and the study protocol would be implemented. The study data would be managed using the data management tools developed for this purpose. Monitoring goals should include identifying safety signals and assessing sentinel events to ensure that study safety and protocol continuity are maintained. Patient accrual progress would be updated in the registry periodically (at least semi-annually, and potentially quarterly). The informed consent process would move forward according to the determinations of the single IRB.

Stage 3: Analysis and Dissemination

At the close of a study, the study outcomes and non-proprietary results (high level) would be promptly disseminated to the transplantation community through peer-reviewed publications and presentations at scientific meetings, regardless of whether the outcomes on the primary endpoints are positive, inconclusive, or negative. D-ROC would receive notice and a copy of all peer-reviewed abstracts and published manuscripts. All reporting would meet the standards of trial reporting (e.g., Consolidated Standards of Reporting Trials; see CONSORT, 2017). Additional dissemination through external newsletters, websites, and public and professional meetings would be encouraged. After a period of time, research teams would, upon request, make anonymous or de-identified individual participant data available to other researchers in order to support meta-analyses and the pooling of results from individual studies. D-ROC could serve as a "learned intermediary" to ensure that patient privacy is adequately protected and that requests for individual participant data have merit (Mello et al., 2013). Each study would be cataloged and archived for future reference. All Health Insurance Portability and Accountability Act (HIPAA) compliance guidelines would be followed when using individual patient data (HHS, 2013; *HIPAA Journal*, 2016).

The goal is for the research results to be used by the donation and transplantation community to improve the quantity and quality of donated organs and thus honor the gift of life provided through deceased donors to improve the lives of transplant recipients.

SUMMARY AND RECOMMENDATIONS

In order to effectively enhance the quality and increase the quantity of donated organs for transplantation, research oversight will be needed to approve well-designed organ donor intervention protocols. To promote feasibility while maintaining the same protections that would hold in other research realms, the committee recommends an organizational structure to oversee deceased organ donor intervention research planning, approval, implementation, and reporting.

GOAL 5: ***Establish centralized management and oversight of organ donor intervention research in order to ensure equitable, transparent, and high-quality research.***

RECOMMENDATION 5: The Organ Procurement and Transplantation Network, in collaboration with the National Institutes of Health, the Health Resources & Services Administration, organ procurement

organizations, donor hospitals, transplantation centers and programs, professional associations, patient advocacy organizations, community representatives, and other relevant organizations, should establish and sustain a standing Donor-Research Oversight Committee (D-ROC) to guide, coordinate, evaluate, prioritize, and disseminate research on deceased organ donor interventions. D-ROC should include the administrative structure to establish independent data safety monitoring boards to ensure the scientific integrity of organ donor intervention research and assess its risks and benefits as studies progress. A single institutional review board should be established or contracted with to ensure human subject research protections for donor intervention research studies.

GOAL 6: ***Promote transparency regarding organ donor intervention research and enable the implementation, tracking, and analysis of organ donor intervention research to improve transplantation outcomes.***

RECOMMENDATION 6: The Donor-Research Oversight Committee, in collaboration with the Organ Procurement and Transplantation Network, the National Institutes of Health, the Health Resources & Services Administration, professional associations, organ procurement organizations, patient advocacy organizations, and transplant centers and programs should create organ donor intervention research electronic tools to ensure that organ donor intervention studies are listed on a publicly available website, that clinicians have the information to provide to potential recipients, that researchers can conduct studies effectively, that research outcomes are tracked and monitored appropriately, and that research outcomes are widely available in aggregate. These tools could use or link to new or current relevant databases but should, at the minimum, provide the following functions:

- **Access to real-time study information used to maintain study continuity and monitor key elements of active studies necessary for project management;**
- **Additional data fields in UNet and other relevant databases to allow for the designation of the organ as a research organ and to note other relevant information about the research protocol for clinical use and in the tracking of research outcomes;**
- **An online registry of pending, approved, active, closed, and discontinued organ donor intervention research studies; and**
- **Links to research outcome data, abstracts, and scientific publications.**

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Meeting Agendas

Committee on Issues in Organ Donor Intervention Research

First Committee Meeting

September 29, 2016
National Academy of Sciences Building
2101 Constitution Avenue, NW, Washington, DC, Room 125

AGENDA

OPEN SESSION

11:30 a.m. – 1:00 p.m.	**Context for the Study** **Panelist Presentations** *Sandy Feng, University of California, San Francisco* *Pete Abt, University of Pennsylvania* *Alex Glazier, New England Organ Bank* *Kate Heffernan, Verrill Dana, LLP (via Webex)* **Committee Discussion with Panelists**
1:00 – 2:00 p.m.	**LUNCH**

2:00 – 4:00 p.m.	**Discussion of the Charge to the Committee** **Perspectives from Study Sponsors**
	American Association for the Study of Liver Diseases American Society of Transplant Surgeons *Tim Pruett, University of Minnesota* American Society of Transplantation *David Nelson, INTEGRIS Baptist Medical Center of Oklahoma* Association of Organ Procurement Organizations *Elling Eidbo* Laura and John Arnold Foundation *Sam Mar* National Heart, Lung, and Blood Institute *Gail Weinmann* National Institute of Allergy and Infectious Diseases *Jonah Odim* National Institute of Diabetes and Digestive and Kidney Diseases OneLegacy Foundation The Transplantation Society *Nancy Ascher, University of California, San Francisco (via Webex)*
	Committee Discussion with Study Sponsors
4:00 – 4:30 p.m.	**Public Comment**
4:30 p.m.	**Open Session Adjourns**

Committee on Issues in Organ Donor Intervention Research

Second Committee Meeting

December 14, 2016
National Academy of Sciences Building
2101 Constitution Avenue, NW, Washington, DC, Lecture Room

AGENDA

OPEN SESSION

8:30 – 8:40 a.m.	**Welcome and Opening Remarks** *Jim Childress, Committee Chair*
8:40 – 10:10 a.m.	**Panel 1: Impact of Research on Organ Donation, Recovery, and Transplantation** **Facilitator:** *Michele Goodwin, Committee Member*
8:40 – 9:45	**Presentations** • *David Klassen, United Network of Organ Sharing* • *Galen Henderson, Brigham and Women's Hospital* • *Danyel Gooch, Indiana University Health* • *Tim Pruett, University of Minnesota* • *Rick Hasz, Gift of Life*
9:45 – 10:10	**Discussion with the committee**
10:10 – 11:15 a.m.	**Panel 2: Barriers, Opportunities, and Lessons Learned from Organ Donor Intervention Research** **Facilitator:** *Lainie Ross, Committee Member*
10:10 – 10:50	**Presentations** • *Darren Malinoski, Oregon Health & Science University* • *Michael Matthay, University of California, San Francisco* • *Doug Hanto, Vanderbilt University*

10:50 – 11:15	**Discussion with the committee**
11:15 – 11:30 a.m.	**BREAK**
11:30 a.m. – 12:35 p.m.	**Panel 3: Future Approaches to Organ Donor Intervention Research Study Design** **Facilitator:** *Bill Marks, Committee Member*
11:30 – 12:10	**Presentations** • *Tim Schroeder, CTI* • *Bertram Kasiske, Scientific Registry of Transplant Recipients* • *Barbara Bierer, Harvard Medical School*
12:10 – 12:35	**Discussion with the committee**
12:35 – 1:35 p.m.	**LUNCH**
1:35 – 3:05 p.m.	**Panel 4: Ethical and Legal Considerations** **Facilitator:** *Glenn Cohen, Committee Member*
1:35 – 2:40	**Presentations** • *Scott Halpern, University of Pennsylvania* • *Elisa Gordon, Northwestern University* • *Sheila Jasanoff, Harvard University* • *Robert Veatch, Kennedy Institute of Ethics, Georgetown University* • *Jerry Menikoff, Office for Human Research Protections*
2:40 – 3:05	**Discussion with the committee**
3:05 – 3:20 p.m.	**BREAK**
3:20 – 4:35 p.m.	**Panel 5: Public Awareness and Public Trust** **Facilitator:** *Kenneth Moritsugu, Committee Member*
3:20 – 4:10	**Presentations** • *Michael Carome, Public Citizen* • *Jim Gleason, Transplant Recipients International Organization* • *Jack Lynch, Gift of Hope*

	• *Laura Siminoff, Temple University (via Webex)*
4:10 – 4:35	**Discussion with the committee**
4:35 – 5:00 p.m.	**Public Comment—Registered Speakers** **Moderator:** *Jim Childress, Committee Chair* (3 minutes per speaker)
5:00 p.m.	**Public Session Adjourns**

Committee on Issues in Organ Donor Intervention Research

Conference Call
Tuesday, January 31, 2017

AGENDA

OPEN SESSION

1:30 p.m.	**Welcome and Opening Remarks** *Bill Marks, Committee Member*
1:35 – 2:15 p.m.	**Committee Discussion** *Tim Pruett, University of Minnesota*
2:15 – 3:00 p.m.	**Committee Discussion** *Elling Eidbo, Associaton of Organ Procurement Organizations* *Jeff Orlowski, Organ Donation Research Consortium*
Approx. 3:00 p.m.	**Adjourn**

Committee on Issues in Organ Donor Intervention Research

Conference Call
February 13, 2017

AGENDA

OPEN SESSION

Welcome and Opening Remarks
Jim Childress and Jim Young

2:00 – 2:30 p.m.	**Committee Discussion** *Tim Schroeder, CTI*
2:30 – 3:00 p.m.	**Committee Discussion** *Dan Schwartz, Centers for Medicare & Medicaid Services*
3:00 – 3:30 p.m.	**Committee Discussion** *Elissa Adair, Donate Life Northwest* *David Fleming, Donate Life America* *Alex Glazier, New England Organ Bank*
Approx. 3:30 p.m.	**Adjourn**

B

Committee Biographical Sketches

James F. Childress, Ph.D. (*Chair*), has been a University Professor, the John Allen Hollingsworth Professor of Ethics, and a professor of religious studies at the University of Virginia, where he is now an emeritus professor. Dr. Childress has previously served as the Joseph P. Kennedy, Sr., Professor of Christian Ethics at the Kennedy Institute of Ethics at Georgetown University and as a visiting professor at The University of Chicago Divinity School and Princeton University. In 1990 he was named Professor of the Year in the Commonwealth of Virginia by the Council for the Advancement and Support of Education, and in 2002 he received the University of Virginia's highest honor, the Thomas Jefferson Award. In spring 2010 he held the Maguire Chair in American History and Ethics at the Library of Congress. Dr. Childress is the author of numerous articles and several books in several areas of ethics, including *Principles of Biomedical Ethics* (with Tom Beauchamp), now in its seventh edition and translated into several languages. Dr. Childress was vice chair of the national Task Force on Organ Transplantation, and he also has served on the board of directors of the United Network for Organ Sharing (UNOS), the UNOS Ethics Committee, the Recombinant DNA Advisory Committee, the Human Gene Therapy Subcommittee, the Biomedical Ethics Advisory Committee, and several data and safety monitoring boards for National Institutes of Health clinical trials. He was a member of the presidentially appointed National Bioethics Advisory Commission (1996–2001). Dr. Childress is a member of the National Academy of Medicine, and he has chaired several studies at the National Academies of Sciences, Engineering, and Medicine. His current research focuses on public bioethics, on public health ethics, and on

just-war theory and practice. Dr. Childress received his B.A. from Guilford College, his B.D. from Yale Divinity School, and his M.A. and Ph.D. from Yale University.

Diana L. Clark, R.N., M.H.A., retired as the president and chief executive officer of LifeCenter Northwest, the federally designated organ procurement organization (OPO) for the Pacific Northwest. LifeCenter Northwest was accountable for a large and regionally diverse area, serving Washington, Idaho, Montana, and Alaska. This OPO service area presented unique challenges for very remote population centers. Ms. Clark previously served as the first executive director, chief executive officer, and chairperson of the board for the Indiana Organ Procurement Organization. She was the first woman elected as the president of the Association of Organ Procurement Organizations. Throughout her career, Ms. Clark was effective in management, program development, and leadership in health care at Methodist Hospital of Indiana. At the time, Methodist Hospital was the 13th largest private hospital in the United States and the first private teaching hospital to perform heart transplants, which Ms. Clark obtained program approval for and directed for several years. During her career, Ms. Clark served in several capacities, including vice president, directly accountable to the hospital president. In these capacities she had accountability for diverse areas in health care—including transplantation, organ procurement, medical education, medical and nursing research, allied health, and community health centers. Ms. Clark is the co-author of the section on donation and transplantation in two editions of *Mosby's Critical Care Nursing* textbook. This is the most widely used critical care textbook for nursing.

I. Glenn Cohen, J.D., is a professor of law at Harvard Law School and faculty director of Harvard Law School's Petrie-Flom Center for Health Law Policy, Biotechnology, and Bioethics. Professor Cohen's current projects relate to big data, health information technologies, mobile health, reproduction/reproductive technology, research ethics, organ transplantation, rationing in law and medicine, health policy, U.S. Food and Drug Administration law, translational medicine, and medical tourism—the travel of patients who are residents of one country, the home country, to another country, the destination country, for medical treatment. Prior to becoming a professor he served as a law clerk to Judge Michael Boudin of the U.S. Court of Appeals for the First Circuit and as a lawyer for U.S. Department of Justice, Civil Division, Appellate Staff, where he handled litigation in the Courts of Appeals and (in conjunction with the Solicitor General's Office) in the U.S. Supreme Court. In his spare time he still litigates, having co-authored an amicus brief in the U.S. Supreme Court for leading gene scientist Eric Lander in *Association of Molecular Pathology v. Myriad*, concerning

whether human genes are patent-eligible subject matter. Most recently he submitted an amicus brief to the U.S. Supreme Court in *Whole Women's Health v. Hellerstedt* (the Texas abortion case, on behalf of himself, Melissa Murray, and B. Jessie Hill). Professor Cohen was selected as a Radcliffe Institute Fellow for the 2012–2013 year and by the Greenwall Foundation to receive a Faculty Scholar Award in Bioethics. He is also a fellow at the Hastings Center, the leading bioethics think tank in the United States. He leads the Ethics and Law initiative as part of the multi-million dollar National Institutes of Health (NIH)-funded Harvard Catalyst, the Harvard Clinical and Translational Science Center program. He is also one of three editors-in-chief of the *Journal of Law and the Biosciences*, a peer-reviewed journal, and serves on the editorial board for the *American Journal of Bioethics*. He serves on the Steering Committee for Ethics for the Canadian Institutes of Health Research, the Canadian counterpart to NIH.

Michele Bratcher Goodwin, J.D., L.L.M., is a Chancellor's Professor of Law at the University of California (UC), Irvine, with appointments at the School of Law; Program in Public Health; Department of Criminology, Law, and Society; Department of Gender and Sexuality Studies; and Center for Psychology and Law. She is the founder and director of the Center for Biotechnology and Global Health Policy at the UC Irvine School of Law and its internationally acclaimed Reproductive Justice Initiative. Professor Goodwin is one of the world's leading authorities on the regulation of medicine, science, and biotechnology. Her publications include 5 books and more than 70 articles and book chapters on law's regulation of the human body, including civil and criminal regulation of pregnancy and reproduction, reproductive technologies, human trafficking (for organs, sex, and marriage), and tissue and organ transplantation. She has been at the forefront of organ transplant discourse, including increasing the supply of organs for transplantation and achieving access across America's many communities. Her recent works appear in or are forthcoming in the *Harvard Law Review*, *California Law Review*, *Georgetown Law Review*, *Northwestern Law Review*, and *Texas Law Review*, among others. Professor Goodwin's scholarship defines new ways of thinking about supply, demand, and access to sophisticated medical technologies. Reviews of her work appear in the *New England Journal of Medicine*, *Nature*, *Publishers Weekly*, *Law and Politics Book Review*, *Book News*, and the *Library Journal*, among other periodicals. Her editorials and commentaries appear in the *Los Angeles Times*, *The New York Times*, *Gene Watch*, *Christian Science Monitor*, *Politico*, *Cleveland Plain Dealer*, *Houston Chronicle*, *Chicago Sun Times*, *The Washington Post*, AlterNet and *Forbes* magazine among others. She is a blogger for the Huffington Post and the Harvard Bill of Health. Professor Goodwin is also the president of the Defense for

Children International U.S. affiliate and founder of the Institute for Global Child Advocacy. She is the former Everett Fraser Professor in Law at the University of Minnesota. She served as a visiting professor at The University of Chicago and as a visiting scholar at UC Berkeley and Columbia University Law School. Prior to law teaching, Professor Goodwin was a Gilder-Lehrman Post-Doctoral Fellow at Yale University.

Jonathan Kimmelman, Ph.D., holds a doctorate in molecular biophysics and biochemistry from Yale University and is an associate professor in biomedical ethics at McGill University, with a cross-appointment in experimental medicine. His research centers on the ethics of translational clinical research. He leads several funded projects investigating risk-benefit across the research trajectory, and he directs the Studies for Translation, Ethics, and Medicine (STREAM) Group. Major publications have appeared in journals, including *Science*, *Lancet*, *BMJ*, and *PLOS Medicine*. His book, *Gene Transfer and the Ethics of First-in-Human Experiments* (Cambridge Press, 2010), is the first full-length analysis of the ethics of translational clinical research and has been described as "set[ting] a new standard for bioethical scholarship that is at once scientifically well-grounded, politically astute, philosophically original, and a pleasure to read." Dr. Kimmelman was the winner of the 2006 Maud Menten New Investigator Prize (Institute of Genetics), received a Canadian Institutes of Health Research New Investigator Salary Award in 2008, and was a Humboldt-Bessel Award Winner in 2014. He has served in numerous advisory capacities, including ethics committee chairs for the American Society of Gene and Cell Therapy (2008–2010) and the International Society of Stem Cell Research (2013–2016).

William H. Marks, M.D., Ph.D., FACS, M.H.A., recently retired from full time employment and currently works as an independent consultant. His immediate past position was executive medical director and global medical lead for transplantation at Alexion Pharmaceuticals (2010–2015). In that role he was responsible for the design and medical oversight of clinical research focused on exploring the safety and efficacy of terminal complement inhibition as a tool to facilitate organ transplantation in patients sensitized to their donors and to protect organs from organ preservation injury. Currently he is adjunct professor of natural products chemistry at the University of Illinois College of Pharmacy. Dr. Marks is a former national medical advisor for the Association of Organ Procurement Organizations and was a founding officer of the board for LifeCenter Northwest Organ Procurement Organization in Seattle, where he also served as medical director for 9 years. He chaired or served as a member of numerous national and local committees related to transplantation, authored more than 100 medical/scientific publications and has received several honors

including the University of Illinois Margaret Wright Graduate College Distinguished Alumnus Award (2007). Dr. Marks received his B.S. and M.D. from Loyola University of Chicago in 1970 and 1977 respectively, his M.S. from the University of Illinois College of Pharmacy in 1973, his Ph.D. from the University of Lund, Sweden, in 1984, and his M.H.A. from University of Southern California, School of Policy Planning and Development in 2009. Dr. Marks did his general surgery residency and transplant fellowship at the University of Michigan. He held academic positions at the University of Michigan, Loyola University, and Yale University. In 1993 he founded the multidisciplinary program in organ transplantation and the laboratory for transplantation biology at the Swedish Medical Center where he held the Robert B. McMillen Chair in transplantation.

Kenneth Moritsugu, M.D., M.P.H., FACPM, is the chairman and chief executive officer of First Samurai Consulting, LLC. He served for 37 years as a career officer in the U.S. Public Health Service. He is a former Surgeon General of the United States (Acting) and has held several public health leadership positions with Johnson & Johnson, including WorldWide Chairman of the Johnson & Johnson Diabetes Institutes and Vice President for Global Professional Education and Strategic Relations for Johnson & Johnson's Diabetes Solutions Companies. Board certified in preventative medicine, Rear Admiral Moritsugu earned a B.A. in classical languages from the University of Hawaii in 1967, an M.D. degree from The George Washington University in 1971, and an M.P.H. from the University of California, Berkeley, in 1975. He holds fellowships in the American College of Preventive Medicine, the Royal Society of Public Health, the Royal Society of Medicine, and the National Academy of Public Administration. He is an adjunct professor of global health at The George Washington University Milken School of Public Health and an adjunct associate professor of preventive medicine at the Uniformed Services University of the Health Sciences.

Glenn F. Pierce, M.D., Ph.D., is a retired biotech executive, volunteer, and biopharma consultant. Dr. Pierce currently serves on the World Federation of Hemophilia (WFH) board of directors and the National Hemophilia Foundation (U.S.) Medical and Scientific Advisory Council. He is an entrepreneur-in-residence at Third Rock Ventures and a board member of Global Blood Therapeutics and Voyager Therapeutics, as well as an advisor to biotechnology companies in the gene therapy and hematological space. Dr. Pierce retired in 2014 from Biogen, where he most recently led the Hematology, Cell and Gene Therapies division as senior vice president. He had overall research and development responsibiliity for hemophilia and hemoglobinopathies and led the development of extended half life FVIII and FIX Fc fusions as chief medical officer, hematology, culminating

in regulatory approvals for both products in 2014. At Biogen, Dr. Pierce spearheaded the initiation of the Humanitarian Aid collaboration with WFH to donate 1 billion units of clotting factor to the low socioeconomic countries, and My Life Our Future, a population-wide genomic biobank initiative in the United States. Dr. Pierce has 30 years of experience in biotechnology research, development, and translation from the bench to the bedside in small and large, public and private biotech and biopharma firms, including Amgen, Avigen, Bayer Healthcare, and Biogen. He is the author of more than 150 scientific papers and holds numerous patents. For more than two decades Dr. Pierce served on the medical and scientific advisory council and the board of directors of the National Hemophilia Foundation (U.S.), where he also served as president of the board. Dr. Pierce served on the Blood Products Advisory Committee at the U.S. Food and Drug Administration and the Committee on Blood Safety and Availability at the U.S. Department of Health and Human Services. He received an M.D. and a Ph.D. in immunology, both from Case Western Reserve University in Cleveland, Ohio, and did his postgraduate training in pathology and hematology research at Washington University in St. Louis, Missouri. He lives in San Diego and focuses his free time on humanitarian aid training workshops in the developing world with WFH. Dr. Pierce was born with severe hemophilia A and was cured in 2008 following a liver transplant.

Lainie Friedman Ross, M.D., Ph.D., is the Carolyn and Matthew Bucksbaum Professor of Clinical Medical Ethics; a professor in the departments of pediatrics, medicine, and surgery at The University of Chicago; and the associate director of the MacLean Center for Clinical Medical Ethics. Dr. Ross has published two books on pediatric ethics: *Children, Families and Health Care Decision Making* (Oxford University Press, 1998) and *Children in Medical Research: Access versus Protection* (Oxford University Press, 2006), and she has co-authored two books with Robert M. Veatch (*Transplantation Ethics*, 2nd edition, Georgetown University Press, 2015; and *Defining Death: The Case for Choice*, Georgetown University Press, 2016). Dr. Ross has also published more than 150 articles in peer-reviewed journals in the areas of pediatric ethics, transplantation ethics, research ethics and genetics and ethics. Dr. Ross earned her A.B. from the Woodrow Wilson School of Public and International Affairs at Princeton University (1982), an M.D. from the University of Pennsylvania School of Medicine (1986), and a Ph.D. in philosophy from Yale University (1996). She did her pediatric residency at the Children's Hospital of Philadelphia (1986–1988) and at Columbia University (1988–1989). Dr. Ross was a 2014 recipient of a John Simon Guggenheim Memorial Foundation Fellowship and the 2015 recipient of the William Bartholome Award in Ethical Excellence from the American Academy of Pediatrics.

Robert D. Truog, M.D., is the Frances Glessner Lee Professor of Medical Ethics, Anaesthesia, and Pediatrics at Harvard Medical School, where he serves as director of the Center for Bioethics, leading teaching and academic initiatives across the medical school, including an undergraduate curriculum, master's degree and fellowship programs, and a post-doctoral program for research scholars. He has practiced pediatric intensive care medicine at Boston Children's Hospital for more than 30 years, including serving as chief of the division for more than a decade. He has published more than 250 articles and books in bioethics and related disciplines, including *Talking with Patients and Families about Medical Error* (Hopkins, 2010) and *Death, Dying, and Organ Transplantation* (Oxford, 2012). In 2013 he was honored with the Spinoza Chair at the University of Amsterdam.

Peter A. Ubel, M.D., is a physician and behavioral scientist whose research and writing explores the mixture of rational and irrational forces that affect our health, our happiness, and the way society functions. Dr. Ubel is the Madge and Dennis T. McLawhorn University Professor of Business, Public Policy and Medicine at Duke University. His research explores controversial issues about the role of values and preferences in health care decision making, from decisions at the bedside to policy decisions. He uses the tools of decision psychology and behavioral economics to explore topics like informed consent, shared decision making, and health care cost containment. His books include *Pricing Life: Why It's Time for Healthcare Rationing* (MIT Press, 2000) and *Free Market Madness: How Economics is at Odds with Human Nature—and Why it Matters* (Harvard Business Press, 2009). His newest book, *Critical Decisions* (HarperCollins, 2012), explores the challenges of shared decision making between doctors and patients.

James B. Young, M.D., is a professor of medicine and the executive dean of the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University and chairman of the Endocrinology and Metabolism Institute. He also serves as a physician director of the Philanthropy Institute and holds the George and Linda Kaufman Chair in the Heart and Vascular Institute. He is a medical director of the Kaufman Center for Heart Failure, which he and a former surgical colleague established in 1998 at Cleveland Clinic. After joining Cleveland Clinic in 1995, Dr. Young was named head of heart failure and cardiac transplant medicine. He is an internationally recognized heart failure and heart transplant cardiologist with an interest in mechanical circulatory support devices. Dr. Young has participated in more than 150 clinical trials as an investigator and has served as the U.S. principal or co–principal investigator for many multicenter clinical trials. He has published more than 650 manuscripts and several textbooks. A member of many professional associations, Dr. Young served as a board

member and past president of the International Society of Heart and Lung Transplantation and as a board member of the Heart Failure Society of America and the American Society of Transplantation. Dr. Young earned a B.A. with honors in biology from the University of Kansas, where he was a resident of Stephenson Scholarship Hall. He matriculated to Baylor College of Medicine in Houston, where he was awarded his medical degree cum laude and was elected to the Alpha Omega Alpha medical honor society. He completed his clinical training at Baylor Affiliated Hospitals. Dr. Young is a fellow of the American College of Cardiology, American College of Physicians, American Heart Association, and the European Society of Cardiology. He is a diplomat of the American Board of Internal Medicine and the sub-specialty Boards of Cardiovascular Disease and Advanced Heart Failure and Cardiac Transplantation.